Acta Medica Scandinavica

Supplementum 652

Vasodilators in congestive heart failure

Proceedings of a Symposium held in Skovde Sweden, on September 12–13 1980

Edited by Lars Rydén and Thor Björn Conradson

Distributed by The Almqvist & Wiksell Periodical Company Stockholm, Sweden

Acta Medica Scandinavica

originally published as *Nordiskt Medicinskt Arkiv* was founded in 1869 by Professor Axel Key MD In 1901 (from volume 34) this journal was divided into a medical and a surgical section Since 1919 (from volume 52) the medical section has been published under the name of *Acta Medica Scandinavica*

Acta Medica Scandinavica

publishes papers on general medicine mainly from Denmark, Finland Iceland Norway Sweden and the Netherlands Short preliminary reports (not exceeding two pages) will be published at short notice. The papers are published in English French or German Acta Medica Scandinavica is published on a non profit basis

Subscriptions

to Acta Medica Scandinavica (two volumes of six numbers each annually) include free supplements to the current volumes

Subscription Rates

Per annum = two volumes.
In Denmark, Finland Iceland Norway Sweden and the Netherlands Sw cr 400 incl postage. Swedish subscribers add VAT Other countries Sw cr 450 incl postage.

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Subscription Distribution and Advertising

The Almqvist & Wiksell Periodical Company
Gamla Brogatan 26 Box 62
S-101 20 Stockholm I Sweden

Printers

Almqvist & Wiksell
S-751 81 Uppsala Sweden

ISSN 0365-463X

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This Symposium was initiated by Lars Rydén and Thor Björn Conradson, Department of Medicine Kärnsjukhuset, Skövde Sweden, and was arranged in cooperation with CIBA-GEIGY Läkemedel AB and Pfizer AB Sweden.

CG 80124
Göteborgs Offsettryckeri AB, Kungälv 1981

ISSN 0365-463X

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INTRODUCTION

On behalf of the Department of Medicine at Kläm-sjukhuset in Skövde we welcome you all to the meeting "Vasodilators in congestive heart failure". We are particularly glad to have among us three distinguished American Collegues and I would like to take this opportunity to express my gratitude to professors Najam A. Awan, Kanu Chatterjee and Jay N. Cohn for their kindness to participate in our meeting and willingness to share with us their long experience of vasodilating agents as a tool in the management of congestive heart failure (CHF). We are all familiar with their pioneering work in this field of cardiology and we are all eager to know more about their present opinions on this topic.

Our intention with the meeting is to summarize the present knowledge about vasodilators in CHF. A number of years have passed since the first reports in this field were presented and since then a large number of papers have been published. It is my impression that this particular drug treatment has gained more widespread use in U.S.A. than in Europe. Particularly in Sweden we do not think it is used to a large extent. This might depend on lack of information to Swedish cardiologists and we hope that this meeting will improve knowledge among us in this country. We hope that the program today covers the present knowledge about the concept of vasodilators in CHF and that the papers tomorrow will give some ideas of what will come in the near future. Whether the meeting will be successful or not depends not only on the program and the invited lecturers. All participants are responsible in this respect. Relatively long time has been reserved for discussions. An interesting meeting is dependent on a vital discussion. We hope and believe that all of you will help us to create a stimulating climate and make these two days worthwhile remembering.

We will also take the opportunity to express our sincere thanks to CIBA-GEIGY Läkemedel AB and Pfizer AB for their active contribution in the organisation of this meeting and for making it possible to publish the proceedings.

Lars Rydén *Thor-Björn Conradson*

PATHOPHYSIOLOGY

Lars Werkö

Congestive heart failure (CHF) is a syndrome that can be defined in many ways. Although imperfectly understood the fullblown picture of heart failure is the combined effect of the failure of one or both ventricles to deliver adequate amount of blood to the tissues and the resulting reactions from the peripheral circulation both on the venous and arterial side. The general physician recognizes congestive failure through the symptoms that occur as a consequence of the failing ventricle, the physiologist defines it through the hemodynamic alterations caused by the inadequate pump function and the cardiologists nowadays probably prefer a combination of both.

It is important to emphasize that CHF is a dynamic state of affairs and requires time to develop. As the background to the whole syndrome is the failure of the heart to deliver an adequate amount of flow to the periphery it is obvious that increased demand on the heart may precipitate failure while its pump function still may be adequate for resting conditions. The underlying heart disease is also of importance for the main manifestations of heart failure. The patient with untreated arterial hypertension may slowly develop signs of left ventricular failure when his daily activities put increasing demands on the heart function, alternating with nightly rest periods. The previously asymptomatic patient who suddenly develops a large anterior infarction may balance between cardiogenic shock and pulmonary oedema, when the left ventricle looses a large part of its pump function. The right ventricular failure of pulmonary disease or mitral stenosis has still other clinical features which may develop in a varying span of time. For the purpose of this symposium left or combined ventricular failure of diseases compromising the myocardium is of greatest interest, i.e. failure in cardiomyopathies, arterial hypertension and atherosclerotic heart disease. In the following I will confine my remarks to such types of failure.

HEMODYNAMICS

The hemodynamic characteristics of CHF have been studied to a large extent since more exact methods for measurements in patients became available. With increasing sophistication in the procedures possible to use in man the details of the physiological derangements in heart failure have been defined to a very large extent. This is especially true for different expressions of myocardial and ventricular functions while the intricate regulation of the peripheral circulation in the face of decreasing myocardial function still is largely unknown although some data have been obtained enough to allow at least some speculations on what may be of most importance in the dynamic evolution of the different events of heart failure.

The studies of the last decades of patients with heart failure have thus added much to our knowledge regarding details of myocardial performance but the main and most important features of the hemodynamic picture of heart failure are still those that were described in the late 40's and early 50's by Cournand and Richards and their pupils. Increased filling pressures, decreased cardiac output (CO), stroke index and stroke work were demonstrated to be typical for most patients in CHF already then. The nomenclature has changed and terms as preload, afterload, compliance and impedance, have been introduced. Determination of ventricular volume and ejection fraction have added some to our understanding of the development but the statement by Richards in 1947 that failure seems to be more a question of raised filling pressures than low CO still seems true. The introduction of more efficient diuretic therapy since then has altered somewhat the impressions of how failure develops but in the acutely ill, suddenly decompensated patient this statement is as accurate now as it was then.

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*From AB Astra, Södertälje, Sweden

However heart failure may have quite different connotations for the heart (myocardium) and the body

For the body the most important consequence of the failing pump is the many regulatory actions that are set in motion leading to altered distribution of peripheral flow with varying grades of vasoconstriction in different areas. The regional flow to vital areas may thus especially in the acute situation be of greater importance than the total blood flow

For the heart on the other hand the speed of contraction and ejection, wall thickness wall stress and the ventricular volume are much more important than the total amount of blood expelled at each contraction or over time.

It is thus important not to look only on CO and the derived peripheral resistance when discussing congestive failure and its treatment. The way all nervous and hormonal influences may act and may be altered during treatment may be more important than the pharmacological profile of a certain drug to be used.

SYMPTOMS

The symptoms of heart failure are more due to the different compensatory mechanisms that are set into play to compensate for the decreased pump function than to the decreased delivery of flow per se. Fluid retention with oedema – pulmonary or systemic – is due to the changes in the renal handling of sodium and water as a consequence of decreased renal blood flow increased sympathetic discharge and secretion of renin. The increased venous pressure behind the failing ventricle is also dependent on increased sympathetic activity and on increased plasma or fluid volume. The increased impedance to flow is also due to reflex vasoconstriction mediated through α-adrenergic impulses.

The details in the complex mechanisms leading to these consequences of the inadequate CO and/or raised filling pressures are still largely unknown. Increased sympathetic activity is certainly of importance as a regulatory measure. This may act both by increasing the force of contraction of the still intact myocardium and by maintaining arterial blood pressure in face of the reduced CO typical for most instances of heart failure.

In severe CHF and especially in its chronic these regulatory activities may be excessive an lead to a vicious circle and causing severe sym rather than supporting the heart in its pump fun

TREATMENT

The treatment of the patient with CHF has u been mostly aimed at the relief of symptoms than at the primary myocardial weakening. I context it should be remembered that Whithen troduced the use of digitalis for the treatment of sy i.e. as a diuretic rather than a cardiotonic a Even today several question the use of digitalis cosides for improving the cardiac contraction i tients with sinus rhythm. The dramatic effect of and sustained digitalization in patients with failu atrial fibrillation is more due to its slowing actio the heart beat than on its weak positive inotropic e That acute digitalization in patients with sinus rhy in acute left ventricular failure both increases CO reases venous congestion and lowers peripheral ance was shown already early when heart cath ization became available for clinical studies. Th ming of these different effects of digitalis in th tients makes it impossible to know what is pri and what is secondary So far the positive inot effect has been thought to be the primary act

The introduction of the thiazide diuretics and ably still more important the loop diuretics changed the whole natural history of congestive fa and its treatment These efficient diuretics – a at the relief of the most important symptom of failure – have become the first line treatment and the one most easily to continue for ever Since use of these diuretics has become common the blown picture of congestive failure has become

What is now dominating the clinical scene is has become known as pump failure in acute cardial infarction (AMI) – rather a variant of what earlier called forward failure. There are also a ce number of patients with intractable congestive fa where the general picture of elevated filling pressu low CO and contracted peripheral vascular bed increased peripheral resistance to flow dominate

...structure. It is in these instances that the new idea has ...been introduced of relieving the heart of the burden ...of pumping against increased resistance by lowering ...it through the use of vasodilators. The efficacy of this treatment and its proper place is one of the main topics of this symposium.

The concept of decreasing the resistance to outflow and at the same time decreasing the inappropriately increased filling pressure of the ventricles has been proposed before. At that time it was not as a reason for using vasodilators but for the use of ganglionic or -adrenergic blocking agents. It is true that the use of arfonad, a short acting sympathetic blocking agent, mostly was recommended and tried out in severe left ventricular failure with pulmonary oedema. It was remarkably effective in reducing both preload and afterload. It must only be due to the relative inconvenience in its use at a time when continuous monitoring of the hemodynamics of the severely ill patient was not routinely used that it never caught on as a way of treatment. A comparison to the acute effects of the presently popular vasodilators might be of interest.

THE AIM OF TREATMENT

It may be a truism to state that the aim of treatment of congestive failure should be to restore the pumping ability of the ventricles, increase CO, correct the increased filling pressures, counteract the excessive reflex vasoconstriction and decrease the increased peripheral resistance (leading to increase of renal blood flow). This is usually not possible as the syndrome does not appear in its full scale until the myocardial reserves are almost totally consumed. What is then of greatest importance – increased blood flow or decreased filling pressures? Already in 1947 Richards stated that congestive failure is more a consequence of increased filling pressure than decreased blood flow. This is still true. The aim of treatment thus has not to be only to increase flow.

As long as the total hemodynamic picture is changed towards normal to such an extent that the stimuli to inordinate counter measures, mostly from the peripheral and renal circulation, are removed the patient will improve.

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EPIDEMIOLOGY

*J. Anders Vedin, Claes Wilhelmsson, Henry Eriksson and Kurt Svärdsudd**

Congestive heart failure (CHF) is not a nosological entity. It represents a clinical syndrome which may be caused by a number of different underlying diseases. In its earliest and mildest form CHF may only cause dyspnea on effort but may progress to a state with generalized anasarca and dyspnea at bed-rest. These factors complicate the study of CHF epidemiology.

The aim of the present report is to extract some available information regarding CHF risk factors, prevalence, incidence and prognosis.

DEFINITION

Congestive heart failure is often defined in hemodynamical therms, e.g. a CO insufficient to meet the demand of the various systems of the body. Such a definition is unsuitable for epidemiological use. In epidemiology, e.g. in population surveys, clusters of symptoms must be defined that, when combined, produce clusters of patients with a high prevalence of CHF.

Most diseases start with vague symptoms and signs. As the condition progresses, more specific symptoms and signs occur. The aggregation of the more specific symptoms and signs make the clinical picture more well-defined. Early (vague) symptoms tend to have a high sensitivity and low specificity and later and more specific symptoms a higher specificity but lower sensitivity.

In the total population advanced cases are rare and the majority of cases are seen during early or intermediate stages of the syndrome. Epidemiology of CHF becomes practical only for early and intermediate stages of the syndrome.

In order to define patients likely to suffer from CHF several symptoms, signs and questionnaire response patterns have been used in different studies (Table I). The definition of the condition should ideally be based on as simple and reproducible measurements and observations as possible. In some studies when CHF patients are defined by subjective symptoms reproducibility may be poor. When more objective signs are used the methods of different studies may also not be comparable. Therefore, widely varying results have been obtained. In fact any result becomes meaningless without meticulous attention to all the details of the definitions. In view of the uncertainty of comparability regarding the details of methodology it is more often than not impossible to compare the results from different studies. The lack of agreement on acceptable and good methods for definition of CHF patients further increase these difficulties. The great span of the clinical symptomatology further tend to make inter-study comparisons difficult even when similar but not identical definitions have been applied. Also, different methods and definitions should be applied for different aims.

Most of the reports in the literature have dealt with circumscribed populations from which no estimates

Table I. Symptoms and signs used in various epidemiological studies in definition of patients with CHF

Dyspnea on exertion
Paroxysmal nocturnal dyspnea or orthopnea
Treatment with digitalis and/or diuretics
Physicians judgement
Acute pulmonary oedema
Neck vein distension
Increased venous pressure >16 cm H_2O
Heart rate and/or rhythm
Heart size (x-ray)
Rales
Respiratory rate
S_3 gallop
Hepatomegaly
Oedema

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**From the Department of Medicine, Östra Hospital, Gothenburg, Sweden*

of the prevalence of cardiac failure either in the hospital or the total community can be made. Since there is inadequate information about the characteristics of each selected population in most of these studies and almost no information about the population at risk they cannot be used for epidemiological analyses ill rected towards the problem of cardiac failure in the community (Klainer *et al* 1963).

RISK FACTORS FOR CHF

A few studies have dealt with risk factors for the development of CHF. In the Framingham study (McKee *et al* 1971) CHF was diagnosed by means of combinations of symptoms from Table I. Definite CHF was diagnosed if two major or one major and two minor criteria were present. The major criteria comprised orthopnea, neck vein distension, rales, cardiomegaly, acute pulmonary edema, S_3 gallop, increased venous pressure and the minor criteria some of the less specific symptoms and signs from Table I. To be accepted minor criteria could not be attributable to any other condition. Hypertension was the dominating precursor of CHF regardless of whether rheumatic heart disease or ischemic heart disease was present as well. The second most common precursor was a combination of hypertension and ischemic heart disease followed by ischemic heart disease alone and rheumatic heart disease. All together hypertension

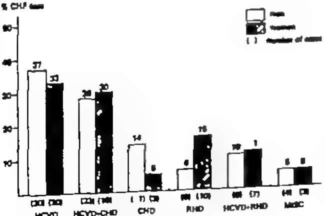

Figure 1. Risk factors for CHF. Results from the Framingham study according to McKee *et al* (1971).
HCVD = hypertensive cardiovascular disease.
CHD = coronary heart disease.
RHD = rheumatic heart disease.
(Printed with permission of N Engl J Med)

preceeded CHF in 75 per cent of the cases and ischem heart disease in 40 per cent (Figure 1) (McKee *et* 1971).

In one study of men born in 1913 the presence atrial fibrillation and/or digitalis treatment was fined as CHF in 1973. The majority of cases had isc mic heart disease (IHD) or hypertension as underly causes. Cardiomegaly (x ray) in 1963 and dyspnea 1967 were significant risk factors for CHF diag in 1973 (Table II). Heart rate was not an risk factor. The sensitivity of the two symptoms taken alone was about 25 per cent and specificity per cent. The sensitivity of a combination of cardic megaly and dyspnea was 35 per cent. When u was present in 1967 the sensitivity was about 55 cent (Table III) (Wilhelmsen *et al*. To be published). In populations with a higher prevalence of pulmonar disease causing dyspnea totally different figures be expected.

Table II. Significance levels for linear relationships some variables and congestive heart failure (CHF) in 1 (Wilhelmsen *et al*. To be published)

Year	Factor	Relationship between variable and CHF p =
1963	Dyspnea	0.86
	Heart rate	−0.56
	Heart volume	0.03
1967	Dyspnea	0.05
	Heart rate	0.22
	Heart volume	0.01
1973	Dyspnea	0.0001
	Heart rate	0.20

Table III. Sensitivity and specificity for some variables used for predicting congestive heart failure (CHF) in 1973 (Wilhelmsen *et al*. To be published)

Year	Factor	Sensitivity %	Specifici %
1963	Dyspnea	26	77
	Heart rate > 85/min	6	91
	Heart volume > 455 ml/m^2	26	85
	Dyspnea & Heart volume > 455 ml/m^2	35	80
1967	Dyspnea	54	70

CONCURRENT DISEASES

In addition to hypertension, IHD and rheumatic heart disease mentioned above, diabetes, chronic lung disease and stroke were often seen in patients with CHF in the Framingham study. Only 40 per cent of the men and women were actually free of major non-cardiac chronic debilitating disease at the time of onset of CHF (McKee et al. 1971). Similar observations have been made in the Swedish population below 60 years of age (Wilhelmsen et al. To be published).

PREVALENCE

In the Swedish population, during the sixties and early seventies, digitalis treatment was first choice therapy for management of heart failure and atrial fibrillation. In the total population in the majority of cases digitalis was administered for management of heart failure and less frequently in management of atrial fibrillation without CHF. Cross-sectional population studies have found prevalence rates strongly increasing with age. The prevalence of digitalis treatment increased from 1 per cent among 54 years old men to 8 per cent among 60–64 year old men (Figure 2) (Elmfeldt 1974). Similar figures have been found also in other studies from the same area. There may also be some secular changes since those figures indicate trend towards a higher prevalence in 1973 than 10 years previously (Table IV).

Age is highly associated with the prevalence and incidence of CHF especially in the Western World. In one study of subjects, 70 years of age, the CHF definition was based on the symptom clusters in Table V. The prevalence of digitalis therapy was 13 per cent

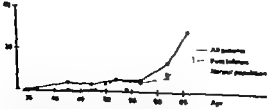

Figure 2. Prevalence of digitalis treatment in Gothenburg, Sweden. Patients with first myocardial infarction (—), all patients with myocardial infarction 1968–1970 (——), sample of the total population (⊕).

Table IV. Prevalence of digitalis treatment in different male cohorts, Gothenburg, Sweden

A. Longitudinal Survey. Men born 1913	
Age	Prevalence (%)
50	0 4
54	0 8
60	4 4
B. Cross-sectional Survey 1973	
Age	Prevalence (%)
30	0
50	1.3
60	5 4

Table V. Definition of CHF among men and women 70 years of age (Landahl et al. 1980).

Cardiomegaly (x-ray) and two of the symptoms cyanosis, dyspnea on exertion and edema
Cyanosis and dyspnea on exertion and edema
Pulmonary congestion (-ray)
Cardiomegaly (-ray) without hypertension

Table VI. Prevalence of cardiac failure and pulmonary disease (%) among 70-year old men and women according to Landahl et al. 1980.

	Males		Females	
	dyspnea (n = 203)	no dyspnea (= 243)	dyspnea (n = 236)	no dyspnea (n = 282)
CHF	33	19	36	13
	26		23	
Pulmonary disease	44	24	20	13

of this population. Only 3 per cent had atrial fibrillation and thus the majority had been given treatment due to signs of CHF (Landahl et al. 1977). In the same study the total prevalence of CHF was 26 per cent among males and 23 per cent among females. Dyspnea was seemingly more associated with CHF than pulmonary disease since prevalence differences between dyspnoic and non-dyspnoic subjects were greater for CHF than for pulmonary disease (Table VI) (Landahl

et al 1980) These figures are, however slightly in contrast to the statement from the same authors that in only some 13 per cent of the population digitalis treatment was indicated This discrepancy is perhaps partly explained by the fact that severe cardiac dyspnea on exertion per se did not constitute a digitalis indication in the absence of absolute cardiac enlargement

Some indications of the amount of cardiac failure in hospitals can be obtained from hospital admission data. These studies, however refer to hospital admissions and not to individual patients and are of limited value in determining the dimensions of the problem in the general population The extent to which reporting is complete, and diagnoses accurate, probably varies considerably These data, therefore, should be interpreted with caution.

Hospital admissions for cardiac failure have totalled approximately 1–2 per cent of total admissions for selected hospitals in Australia, Canada and the United States. The proportion of admissions appears to be less in hospitals in England and Wales. It is not clear whether these figures represent "real" differences. If the differences are "real" it would be important to establish whether they are due to variations in the kinds of heart disease prevalent or in the recognition of the clinical syndrome by patients or physicians, the availability and adequacy of medical care, or other factors. These data are percentages of total hospital admissions and community prevalence rates for all cardiac failure in the general population cannot be derived from them (Klainer *et al* 1965).

A study of morbidity seen in general practice was undertaken in England and Wales by the College of General Practitioners and the General Registrar Office. This was based on the clinical records of 171 general practitioners in 106 practices The physicians were selected so that the patients they served would collectively be representative of the population of England and Wales for the 12 month period May 1955–April 1956 The rates at which patients with CHF and left ventricular failure consulted their doctors during the survey period regardless of when the illness began, how long it lasted or how many visits were involved, for different ages are shown in Table VII In these studies, however specific definitions of CHF comparable to the studies presented above, are not available (Logan & Cushon 1958).

Table VII Observed percentage prevalences of CHF for both sexes reported from general practitioners offices.

Author	Year	Country	Age (years)	
			45–64	65–
Logan *et al*	1958	U.K.	0 2	1 9
Gibson et al	1965	U.S.A.	0 9–1.2	6 5

Six month surveys in two United States counties were conducted in which all physicians both within and surrounding the counties participated. By this method it is believed that virtually all patients residing in these two counties who might have had CHF were identified if they were seen by a physician during the study period Because of the relative stability of the populations in both counties, and the geographical areas involved it is likely that very few patients within the counties were not identified by the physicians Thus, differences were again demonstrated between Europe and the USA but again are impossible to interpret (Table VII) (Gibson *et al* 1965).

In the Evans County Study during 1960–1962 approximately 90–94 per cent of the study population between the ages of 15 and 74 were examined and the prevalence rates for CHF were 1 7 per cent for the 45–64 age group and 3.5 per cent for the 65–74 age group. The total prevalence rate for ages 45–74 was 2.1 per cent This is probably too low a figure for the entire population, since there were 274 people over the age of 74 who were not examined (McDonough *et al.* 1965 Klainer *et al* 1965).

Thus, very large differences were revealed when the prevalence of CHF was studied in different countries and regions. Obviously different definitions and methods account for some part of the difference observed. Whether other factors are also important cannot easily be analyzed

In the Framingham study 17/5209 men and women on entry had signs of CHF giving a crude prevalence for that age structure of 0 3 per cent However the prevalence of CHF is strongly age related and no subject was older than 62 years (McKee *et al* 1971). Here another important factor becomes apparent explaining the scant epidemiological literature in the field – most epidemiological studies have been restricted to too young age groups.

INCIDENCE

In the Framingham study of the 5192 men and women at risk of developing CHF during the 16-year period of the Framingham Study 142 acquired the disease. Table VIII shows the average annual incidence of CHF according to age and sex. The incidence was far from trivial 3.5 per cent of the men and 2.1 per cent of the women developed overt myocardial insufficiency. The annual rate was 2.3 per 1000 for men and 1.4 per 1000 for women. Advancing age was a major factor in the development of CHF. The incidence in men in their sixties was five times that of men in their forties. Women also reflected an increased incidence of CHF with age (McKee *et al.* 1971).

Incidence studies are not easily available from other areas. Obviously countries with endemic cardiac infections, e.g. Chagas disease may be expected to produce high incidence rates.

Table VIII. Average annual incidence of CHF according to age and sex. Framingham Heart Study. 16 year follow-up results (rate/1000/year) (McKee et al. 1971)

	Men	Women
All ages	2.3	1.4
29–34	0.8	
35–39	0.6	
40–44	0.4	0.6
45–49	0.9	0.2
50–54	3.0	1.1
55–59	3.7	1.6
60–64	4.1	4.1
65–69	5.3	4.2
70–74	8.7	3.0
75–79		

PROGNOSTIC IMPORTANCE

Regardless of underlying cause or clinical stage CHF always negatively affects the prognosis. This is true for hypertension, acute and chronic IHD and valvular heart disease. Although conventional management may change the short term outcome long term mortality remains high once CHF has become manifest. It should be clarified that this is not a result of CHF per se but a result of the functional capacity and reserve of a myocardium suffering from a progressive disorder. CHF only reflects a point in the natural history when compensatory mechanisms become insufficient.

CONCLUDING REMARKS

In western industrialized countries IHD and hypertension are highly associated with CHF. The prevalence and incidence are both strongly associated with age. Detailed information regarding the prevalence and incidence of CHF is lacking. It is also necessary to focus strict attention on the importance of rates in non-attending groups likely to have high rates especially in older populations.

Due to the nature of the syndrome of CHF conventional epidemiological study of prevalence, incidence, risk factors and prognostic implications warrant a special attitude in planning such studies and interpretation of the results. Due to the nosological heterogeneity of the syndrome epidemiological studies of the underlying diseases are likely to be more rewarding.

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Risk factors for CHF

Werkö

Is it really adequate to talk about risk factors for CHF when you are talking about hypertension, IHD or dyspnoea which are diseases or symptoms. Is this a misuse of epidemiological terms rather than an adequate terminology in this context?

Vedin

No not if you stick to the definition of a risk factor as a statistical entity rather than a causal medical factor In other words, it is a factor which is statistically associated with a certain outcome. I think it is important to use it because it enables us to talk about early stages and to define patients where there is high likelihood of future development of CHF

Wilhelmsen

Cardiac failure of severe grades, for example New York Heart Association Class III–IV is very uncommon in the general Swedish population of middle aged men or women. However the prevalence increases with increasing age and we hope to be able to find predictors for the syndrome among an extensive series of variables including maximal exercise test examined at age 50 54 and 60 It is also of interest to see which diseases are the most common causes of CHF in our population with the ultimate aim of finding preventive measures.

Vedin showed that dyspnoea was a predictor of later clinical CHF but dyspnoea was also a predictor of myocardial infarction and angina pectoris in our prospective studies. Thus, it seems as if a middle-aged person with dyspnoea could end up in any of the three manifestations or in combinations. It should be stressed that chronic obstructive lung disease is not too common in this population, about 2 % having asthma with obstruction and about 2 % chronic bronchitis with obstruction.

In the population studies of men and women aged 70 years it has been found that 14 % are on digitalis treatment – some of them probably with the only indication dyspnoea which in turn might be due to monary disease and aging processes in the lungs example giving increased closing volume). T tients do certainly not benefit from digitalis

Werkö

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Wilhelmsen

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Vedin.
My message is that you have to apply a definition which is satisfactory for your particular purpose. You often have to do a special study for the purpose of arriving at a proper definition because there are no general data available in the literature. It may suffice for us to recognise that it is a common and important problem. To advance our knowledge it is much more fruitful to study the natural history of the underlying disease.

Werkö
I think the last thing you said is exactly what you should emphasize. It is meaningless to study CHF in the population at large, because there are so many different etiologies. It might very well be of great interest to study the incidence of CHF in a population of hypertension or in a population of cardiomyopathies or in a population of myocardial infarction. You could use a defined disease and there you could study the incidence.

Cohn
I would like to reverse your approach which suggests that the syndrome of CHF should be looked at more from an etiological standpoint rather than from study of the syndrome itself. My impression has been that CHF becomes a self-perpetuating process in which etiology ceases to be the primary determinant of the natural history. Study of the development of CHF in specific etiologic entities becomes particularly difficult in the cardiomyopathies, the diagnosis of which usually is not made until the patient presents with symptoms of cardiac dysfunction. Rather than focusing on etiology, therefore, I think we need to develop more sensitive and specific tests to detect and follow patients with disturbed left ventricular function to gain more insight into the mechanisms and natural history of the apparently progressive hemodynamic derangement. Such studies would need to pay special attention to such myocardial factors as wall stress and hypertrophy, changes of which may well be independent of primary etiology, as well as to the contributions of the peripheral circulation to aortic impedance.

Does treatment of cardiac disease change the prevalence of CHF?

Mogensen
Over the last decades many different and effective means of treating cardiac disease have been introduced. Could you speculate about the resulting trends in the prevalence of CHF?

Vedin
No, there is not really any evidence to that. The approach to define CHF patients have changed. Dyspnoea at one time and in one population may mean something different from what it was at another location at a different time. We really know very little about time trends on the epidemiology of CHF. Obviously the total prevalence in the population is higher today than it was 20 years ago due to the nowadays longer life-span.

Rydén
Hypertension is a strong predictor of CHF. We are eagerly treating hypertension today. Do you think that a new study of the prevalence of CHF will give quite different results.

Vedin
I think so. If we are enthusiasts and accept the VA findings we can certainly postpone the development of failure. I think that failure is very likely to develop anyway but at a later stage.

Werkö.
Is that really true. Is it not possible to postpone the development of disease to such an extent that the patient dies before he would have developed CHF? If you look at the statistics on mortality in hypertension, CHF almost disappeared as cause of death while it was one of the main causes 30–40 years ago.

Vedin.
So has methods of ascribing causes of death also changed over time. If we look at the primary pre-

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Werkö

Vedin said that there was a high prevalence of other debilitating diseases in the patients who develop CHF Does that mean that patients who develop CHF live long enough to develop this syndrome while people who do not develop CHF die earlier?

Vedin

This is impossible to answer I think that we are at a stage where speculations are available but very few solutions.

How to study the epidemiology of CHF

Rydén

We have been told that it is very difficult to describe the number of people suffering from CHF I find that

disappointing since this is a large clinical problem. Can you give us some idea if we want to study the problem how to aim at the target

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Vedin

So has methods of ascribing causes of death also changed over time. If we look at the primary pre-

ventive trial in Gothenburg it seems that the mortality pattern is really not very much different today than 10 years ago. As a cause of death CHF is not very common. Patients in severe CHF referred for treatment do not die in refractory CHF. They suffer sudden deaths, thus they die from arrhytmias.

Wikstrand

I think you are rather sceptical as regards antihypertensive treatment and the prevention of CHF. In the treatment group of the VA study there was not one single patient with CHF. I think antihypertensive treatment is a very attractive approach to handle the problems of CHF because you can prevent or postpone it. Do you not agree on that point?

Vedin

Yes, provided that we can generalize the findings.

Werkö

It is really quite certain that treatment of hyperten[...] will prevent CHF. On the other hand if you def[...] CHF as a patient with oedema and you treat hype[...] tension with diuretics you still do not exactly kno[...] what kind of end point you are using. This confu[...] the whole issue. The introduction of thiazide diure[...] has changed the picture to such an extent that i[...] difficult to compare the clinical picture of CHF an[...] its epidemiology in the fifties, sixties and seventie[...]

Vedin

I agree. One should be very cautious using the wo[...] prevention, I think postponement is what we are reall[...] dealing with.

CLINICAL DIAGNOSTICS

Bengt W Johansson

INTRODUCTION

Although congestive heart failure (CHF) was unknown, treatment for dropsy one of its symptoms, was practised in ancient cultures. Scilla as a remedy for oedematous patients is mentioned in Papyrus Ebers. The Chinese have long employed the dried preparation from a common toad as a drug. In China, the remedy is known as Ch an su and in Japan as Senso (Movitt 1946). Before the introduction of foxglove, which Withering had unveiled as the active component of a family receipt for the cure of the dropsy which "had long been kept a secret by an old woman in Shropshire (Withering 1785), dried and powdered toad skins were in common use for treatment of dropsy. The beneficial effect of these drugs which contain cardiac glycosides clearly indicates that CHF has been a clinical reality for many years. In fact, Harvey described heart failure when he wrote that in presence of many witnesses, I have demonstrated the right auricle of the heart and lungs distended with blood, the auricle in particular of the size of a large man s fist and so full of blood that it looked as if it would burst.

Many disease states are capable of causing the heart to fail and heart failure is not always produced primarily by failure of the myocardium, but can be elicited in patients with normally functioning heart muscle by for instance, brady or tachyarrhythmias, constrictive pericarditis, and endomyocardial fibrosis. The spectrum of causes of heart failure in the adult population has radically changed over the past few years, rheumatic disease has now been supplanted by the far more frequent syndrome of coronary heart disease (CHD).

Heart failure is that state in which the heart is unable at a normal filling pressure to pump sufficient blood to meet the current demands of metabolically active tissues. Early in the course of heart failure, a number of compensatory mechanisms are brought into play preserving for a time adequate cardiac performance. When these mechanisms wane or become inoperative, a constellation of symptoms and signs emerge, permitting the clinical recognition of heart failure. The late stage of CHF presents itself with a uniform clinical picture. The early stages, however are to a certain extent typical for the disturbances in heart function which produce heart failure. The clinical presentation of heart failure differs substantially in adults and children due to the heart failure in children being usually caused by congenital defects which result in an increasingly heavy burden on a "healthy" myocardium. CHF in the elderly also differs in many respects from what is found in the middleaged and young (Wedgwood 1972). The reasons for this are that some diseases are specific to old age (senile cardiac amyloidosis and the various forms of valvular heart disease specific to the elderly) and some diseases that affect patients of all ages are modified by old age (bizarre presentations of cardiac infarction, bacterial endocarditis presenting with particularly insidious manifestations). This presentation will discuss the general clinical picture of CHF in adults.

SYMPTOMS

Although history yields diagnostically useful information in most patients, predictions from history alone are limited in the case of heart failure by the priority accorded to various symptoms by the patient and the difficulties of prediction of the severity of the functional impairment of the heart from history alone. The priority point is illustrated by the simultaneous occurrence of anginal pain and breathlessness during exercise-induced angina pectoris. As a rule, pain is given overriding priority amongst symptoms. Therefore

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breathlessness is rarely mentioned as a feature of the anginal syndrome although reversible left ventricular failure accompanies the onset of pain.

The second limiting factor namely the prediction of the extent of physiological impairment of cardiac function from a patient s account has been emphasised in textbooks and teaching alike and has resulted in a wide acceptance of the functional and therapeutic classification proposed by the Criteria Committee of the New York Heart Association. Although a consideration of symptomatology is essential for a correct diagnosis, it is now recognized that a classification based on symptoms alone can be misleading. Symptoms might be absent in the presence of serious anatomic or physiologic abnormalities, e.g. septal defect. The seventh edition of the Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels therefore rescinds the functional and therapeutic classification and abandons any attempt at grading the severity of symptoms of heart failure. This is probably to go too far especially if due consideration is taken to the patient s working and leisure activities, as it always should and when there exists a possibility to follow the natural history of disease or the result of a treatment by comparing the patient s ability to perform a defined work with different time intervals, e g. the time it takes to climb a hill or for the golf-player to go nine holes.

Dyspnea

Symptoms associated with CHF are produced by the dysfunction of other organs. Shortness of breath, or breathlessness, or dyspnea, is a common early symptom resulting from a rise in pulmonary venous pressure caused by failure of the left ventricle. Usually breathlessness is confined to awareness of increased breathing by a "healthy" person during exercise whereas dyspnea includes a sensation of difficult labored or uncomfortable breathing. Although breathlessness is the most common early symptom, it is not pathognomonic of heart failure and in a patient it can be produced by more than one disease, e.g. CHF and emphysaema. The long-term effect of pulmonary venous congestion is decreased compliance of the lungs, and an increased airway resistance can occur The net effect is an increase in the work of breathing which manifests itself as dyspnea.

The earliest manifestation is dyspnea provoked only by effort, subsiding entirely with rest. With more advanced failure, dyspnea appears at rest.

Orthopnea is dyspnea decubitus i e. it develops or worsens shortly after assuming the recumbent posture and is relieved by sitting up or standing. Recumbency results in an increased work of breathing in stiff congested lungs. The tendency is aggravated both by the increased venous return and by the pressure beneath the diaphragms in patients with ascites and hepatomegaly In some individuals, a blood pressure drop accompanies the left recumbent position this presumably results in a diminished blood flow with concomitant ischaemic pain and left lateral decubitus dyspnea

This should be differentiated from angina decubitus, i.e. nocturnal angina that is a manifestation of heart failure and occurs irrespective of the recumbent position assumed Typically a patient with daytime angina experiences nocturnal angina that wakes him up after one or two hours of sleep Angina decubitus is a manifestation of heart failure and should therefore be treated with diuretics and digitalis. To the extent that vasodilating agents diminish left ventricular work such drugs can be of benefit to the patient

Paroxysmal nocturnal dyspnea occurs after prolonged recumbency Characteristically the afflicted patient awakens after some hours of sleep and finds it necessary to sit up for relief Paroxysmal cardiac dyspnea is more likely to be produced by interstitial than alveolar pulmonary oedema Persistent elevation of the pulmonary venous pressure leads to the development of a collagen barrier between the capillaries and the alveoli This barrier has a tendency to confine transudate to the interstitial spaces which might in part explain why paroxysmal cardiac dyspnea which is subjectively a less severe form than acute pulmonary oedema, can represent a more advanced stage of the disease. The clinical picture of the attacks are often coloured by the compensatory mechanisms and complicating effects such as coughing and wheezing, substernal tightness (ischaemia), faintness secondary to hyperventilation and manifestations of adrenergic activity such as palpitations, peripheral pallor and cyanosis, cold extremities, profuse sweating and eleva

tion of mean blood pressure. Especially in elderly patients with heart failure who have been given barbiturate sedatives the hyperpneic phase of Cheyne-Stokes respiration can be mistaken for paroxysmal nocturnal dyspnea. Dyspnea due to heart failure can occasionally be difficult to differentiate also from the anxiety breathlessness of hyperventilation. The cardiac dyspnea is characterized by rapid shallow breathing, whereas in anxiety hyperventilation, the patient takes deep sighing breaths and complains that, no matter how deeply he inhales, air hunger is not satisfied.

Acute pulmonary oedema

Acute pulmonary oedema is more likely to occur when the pulmonary venous pressure rises suddenly from a previously normal or only slightly elevated level. The common use of oral diuretics has resulted in a decreased number of cases with acute pulmonary oedema. Although left heart failure is the commonest cause, acute pulmonary oedema can be seen in connection with other diseases, such as disturbances of the central nervous system including trauma to the skull, in some cases due to reflex left heart failure, pulmonary infections, inhalation of irritant gases, drowning, burns, nephritis, drug therapy and overloading the circulation with intravenous infusions. If latent heart failure is suspected, intravenous infusions should be avoided if possible: the same amount of fluid is much better tolerated if given orally than intravenously, even if it is infused very slowly. High altitude pulmonary oedema is an interesting variety that develops as a rare and clearly abnormal response in acute ascent to high altitude. It has been recognized only in humans and is not due to left ventricular failure, left atrial pressure being normal, but possibly to pronounced constriction of the pulmonary veins (Reeves & Glover 1975).

Cough

A subtle but important symptom in CHF is cough. Initially it appears on effort. A typical, but often neglected, early sign in mitral stenosis is the hacking, nonproductive cough during physical exercise; later it appears during recumbency.

Haemoptysis

Haemoptysis is usually a result of bronchial or pulmonary congestion.

Fatigue

A common complaint in patients with CHF is fatigue. It can be a direct consequence of heart failure *per se* being secondary to a low cardiac output (CO), but it can also result from insomnia, nocturia, nocturnal dyspnea or nocturnal cough.

Cardiac cachexia

The final stage of a long standing heart failure is cardiac cachexia.

Systemic oedema

Systemic oedema can be subtle and its inception detected only by comparisons of daily weight. Regular measurement of body weight is a simple and useful check to detect possible water retention in patients with latent heart failure who are given negatively inotropic drugs. Characteristically oedema is dependent except in children in whom the face and abdomen are involved rather than the feet. Early morning depressions of the lace of the pillow-case in the cheek of a woman is therefore a sign of premenstrual water retention rather than heart failure. Curiously enough, oedema is confined to dependent parts of the lower extremities and the back in recumbent cardiac patients, whereas the lower parts of the upper extremities do not become oedematous. Lesser degrees of oedema can be suspected when the patients report that they notice tightness of their shoes or pitting depressions of the feet or legs when socks or garters are removed at the end of the day: this trifling oedema disappears during the night. The ultimate in oedema is anasarca, that is to say a generalized massive oedema including genitalia and thorax; in this stage of heart failure, arms and face can be involved.

Nocturia

Nocturia can be frequent and annoying, seriously interfering with sleep. As oedema forms during day time, plasma volume and renal blood flow decrease, resulting in a diminished urine production. Improvement

of renal blood flow during sleep promotes urine production with concomitant resorption of the peripheral oedema accumulated during the day. Nocturia replaces daytime oliguria.

Ascites

Ascites can sometimes be suspected from the history when a male patient becomes aware of an increased girth requiring a looser belt or purchase of a larger size. The rules of fashion have made cardiac diagnosis more difficult when denouncing the use of girdles. Some years ago when girdles were still in common use, the complaint of a female patient that her girdle no longer fitted comfortably contributed to the correct diagnosis of ascites.

Splenomegaly and hepatomegaly

Right heart failure with raised venous pressure also results in splenomegaly and hepatomegaly. Tenderness of the liver is usually associated with recent or significant increase of existing congestion. However, in some patients with chronic heart failure the fibrous capsule surrounding the liver is a nonexpansile harness resulting in troublesome pain. Hepatic pain and tenderness can be so severe that an acute abdominal condition, such as cholecystitis, can be suspected.

Peripheral cyanosis

Peripheral cyanosis is due to sluggish peripheral circulation with excessive extraction of oxygen by the tissues. This is not always a result of heart failure. A normal arterial oxygen tension is helpful in the differential diagnosis. But it should be kept in mind that an increased tissue extraction of oxygen from systemic capillaries, which is a compensatory mechanism for the diminished tissue perfusion of heart failure, can go with a normal arterial oxygen tension.

Gastrointestinal symptoms

This is something that can accompany CHF. In addition to right upper quadrant or epigastric pain resulting from distension of Glisson's capsule, bowel wall oedema can result from the systemic venous congestion of right ventricular failure and result in anorexia, nausea, abdominal distension and a sense of uncomfortable fullness after meals. Anorexia and nausea can be impossible to differentiate from digitalis intoxication. Digitalis withdrawal will solve the problem. Digitalis plasma concentration can be helpful. Bowel wall oedema can also result in malabsorption of drugs used in the treatment of heart failure. This is especially obvious for diuretics. Large oral doses producing annoying gastrointestinal side-effects have no diuretic effect, whereas a small dose of the same drug given intravenously has a marked effect with abundant urine production.

Fever

Fever is not a result of heart failure *per se*. Especially in acute failure after a myocardial infarction, a protracted, moderate increase of the body temperature is normalized after treatment with diuretics and digitalis. The probable explanation is bronchopneumonia secondary to congestion of the lungs.

Increased adrenergic activity

The increased adrenergic activity in CHF gives rise to several symptoms such as inappropriate perspiration, peripheral pallor and cyanosis, cold extremities, and tachycardia.

SIGNS

Several of the signs of CHF are obvious from the previous section on symptoms. The clinical presentation can vary depending on the rate of development. In acute left ventricular failure after a myocardial infarction, the only abnormal physical sign is perhaps that of a third heart sound; pleural effusion is also a common finding. Opinions differ as to the propensity of fluid to accumulate in the right or left pleura or both. The chronic stage is characterized by additional features, such as dyspnea, dependent peripheral oedema, and finally cardiac cachexia.

Rales

Intra-alveolar fluid produces fine rales characteristically evenly distributed over both basal lung fields. They are often confined to the inspiratory phase because the walls of the alveoli, which are glued together by the sticky transudate, open with a crack during inspiration. Fluid within the lumens of bronchioles and bronchi produces coarser rales and can be difficult

differentiate from bronchial asthma. Wheezing can be the result of narrowing of the lumens of airway walls by oedema. True cardiac and bronchial asthma can exist concomitantly. Interstitial oedema produces no rales at all despite overt dyspnea.

Extra heart sounds

Extra heart sounds, in addition to the normally occurring first and second sounds, can be signs of heart failure. There are two diastolic filling periods in each cardiac cycle: one passive and occurring relatively early in diastole, one active and occurring late in diastole and initiated by the active atrial contraction. These filling periods can be accompanied by sounds, the third and fourth heart sounds, respectively. These can be a normal finding especially in children and young adults up to an age of 35–40 years.

The pathological *third heart sound* is produced by an increase in the rate and volume of atrioventricular flow during the passive filling period and by the altered physical properties of the failing ventricle. Early in the course of ventricular failure, the third heart sound is often soft and inconstant and can be difficult to hear. It is best heard with the patient in the left lateral position and with the bell of the stethoscope, not the diaphragm, lightly attached to the part of the thorax where the left ventricular impulse is palpated. The third heart sound is of low frequency and might be barely audible. It can best be described as the soft pattering of cat paws on the parquet floor. Sometimes it is appreciated as a change of rhythm rather than a discrete sound. Potain's description fits in well when he wrote: "The sound is dull, much more so than the normal sound. It is a shock, a perceptible elevation, it is scarcely a sound. If one applies the ear to the chest it affects the tactile sensation more perhaps than the auditory sense. And if one attempts to hear it with a flexible stethoscope, it lacks only a little, almost always, of disappearing completely."

The pathological *fourth heart sound* is produced in a ventricle that depends more heavily upon atrial contraction to achieve a satisfactory contractile state. This occurs when a ventricle ejects against a high resistance, e.g. in systemic or pulmonary hypertension and aortic or pulmonary stenosis, when decreased ventricular distensibility (compliance) provokes an increase in contractile force of its atrium, e.g., ventricular hypertrophy, ischaemic heart disease or cardiomyopathy. A pathological fourth heart sound alone is not a feature of ventricular failure except when in combination with a pathological third sound. With a prolonged PR interval or a rapid heart rate these two sounds can melt together and create one loud sound. The development of atrial fibrillation results in a disappearance of the atrial contraction and therefore of the fourth heart sound.

Both the third and fourth sounds increase in loudness as a result of exercise by increasing venous return and accelerating heart rate. A few sit ups can suffice. Right ventricular filling sounds are likely to become louder with inspiration, whereas the filling sounds from the left ventricle have a tendency to soften or remain unchanged.

The third sound alone or the fourth sound alone or both these sounds together can, but do not necessarily create a cadence to which the term gallop rhythm has been applied. The term "gallop rhythm" was introduced by Bouillaud and popularized by Potain (1876). However, it is preferable to call these sounds by specific names, e.g., third and fourth sound, or systolic click if this systolic sound contributes to the gallop cadence. The term triple rhythm is perhaps the most appropriate one when it is impossible to analyse with the aid of auscultation the different compounds of the cadence.

Additional auscultatory signs

A number of additional auscultatory signs are found in heart failure. The physiological increase in the splitting of the second heart sound with inspiration disappears when the ventricular stroke volumes become fixed. A pansystolic murmur resulting from interference with apposition of the mitral or tricuspid leaflets can emanate from dilatation of the inflow ring, change in the shape of the ventricle, or the direction of tension exerted by the papillary muscles. Resulting mitral regurgitation produces an apical pansystolic murmur and tricuspid incompetence a pansystolic murmur over the lower left sternal edge.

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Laboratory values

Laboratory values can be influenced by heart failure. Fever has already been discussed. Serum bilirubin and liver transferases, ASAT and ALAT, might rise to pathological levels due to liver congestion. Spotted liver necrosis as an end result of the congestion can elevate ASAT and ALAT values to extremely high levels. By the same token, heart failure can raise the levels of serum alkaline phosphatases and amylase. The sedimentation rate behaves reversely and shows a reduction often below 2 mm/hr. Hypoglycaemia in heart failure has been ascribed to reduced delivery of gluconeogenic substrates to the liver. Loss of weight, decreased food intake and mild hepatic dysfunction are features in common with reported cases (Block *et al* 1972). The symptoms of hypoglycaemia in a cardiac patient can mimic several of the findings of left ventricular failure and shock.

DIAGNOSIS AND COURSE

The diagnosis of CHF rests not on a single symptom or sign described above but, with a different degree of probability, on a cluster of symptoms, physical and laboratory findings. The diagnosis is supported by a beneficial effect of treatment with digitalis and diuretics. CHF might hide behind a reduced physical activity. Conversely, heart failure might be elicited by increased physical activity and also by arrhythmia, infarction, anemia, renal insufficiency, pregnancy, intravenous infusions, sodium retaining or negative inotropic drugs, reduction or withdrawal of digitalis and/or diuretics, or emotional factors (Perlman *et al* 1971).

The course of CHF is not always progressively downhill but periods of deterioration alternate with periods of improvement. Deterioration can occur without any of the eliciting factors listed above, indicating that unknown factors are at work.

In patients with CHF followed over several years and also in patients with a more aggressive course, for example, as in endomyocardial fibrosis (Belfrage *et al* 1965), it is obvious that the clinical condition can alternate periodically, although a clearcut biological rhythm is not discernable. This aspect of the natural history of congestive heart failure is of importance not only to the research worker trying to elucidate the pathophysiological mechanisms or evaluate the therapeutic effect of drugs in heart failure, but also to the doctor who tries to give his dyspneic patient a word of comfort.

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Signs and symptoms

Waldenstrom.

When a patient presents symptoms typical for CHF do you as a clinician have any possibility to judge whether this is due to high filling pressures secondary to lowered distensibility with normal systolic function or if the symptoms are due to systolic disturbances of pump function with low output?

Johansson.

The symptoms of the patients are definitely to a certain extent depending on the underlying disease especially in the early stage of CHF. In more advanced stages the symptoms are independent of the underlying disease.

Werko

Do you really often see patients with enlarged spleen in CHF? That you have a big liver is obvious but do you really have an enlarged spleen, because that is why you think that there is edema in the intestine.

Johansson

It is more difficult to palpate an enlarged spleen than an enlarged liver. I am quite sure that if you more systematically follow these patients by subtle diagnostic instruments, for example X-ray you would find the spleen enlarged in many patients, although you are not able to palpate it.

Chatterjee

Radioisotopes have shown that the spleen is enlarged in patients with CHF.

S edberg

In the evaluation of CHF the third heart sound is certainly important. The prevalence of the third heart sound different age groups is not known. I do not think that it is a normal finding at 35–40 years. I only know one investigation where the prognostic implication of the third heart sound has been studied and that the study from Massachusetts General Hospital here they studied the prognosis after non-cardiac surgery (Goldman *et al.* 1977). The third heart sound or jugular ein distension was as important as a myocardial infarction during the last six months. I think the due of the third heart sound has to be studied further.

Johansson

My lack of knowledge was the reason for setting the age limit that high.

Drug absorption and CHF

Rydén

It has been claimed that it is impossible to develop an intestinal edema. You said that during the treatment of CHF it might be worthwhile putting patients on parenteral rather than oral treatment because they do not absorb tablets. Is this due to edema or altered circulation in the intestine.

Johansson.

We have not done biopsies trying to confirm the existence of edema or not. An important but pure clinical experience is that several patients with a pronounced CHF do respond much better to intravenous diuretics than to oral. My conclusion has been that as there is an edema in the legs, a swollen liver and an enlarged spleen, why should there not be edema in the intestinal wall?

Andersson.

I think there are several explanations to a better response after intravenous administration of for example furosemide than following oral ingestion. Furosemide is incompletely absorbed (biological availability about 50 %) and in a patient where you really need a diuretic response this incomplete absorption could be of importance. I think that it is very difficult to predict the effect of CHF on the absorption of drugs. Generally a slowing of absorption rate can be expected, but it is not possible to predict if the extent of absorption is diminished. It has been stated that digoxin is poorly absorbed in CHF. However this drug is absorbed at a lower speed. The extent of absorption is not diminished.

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RADIOLOGICAL DIAGNOSIS

Ulf Tylén

The radiological diagnosis of congestive heart failure (CHF) is based on changes in the size of the heart and of the pulmonary circulation.

Enlargement of the heart is usually quite easy to recognize. Although there are elaborate methods for calculation of the size these methods have many sources of error and generally there is seldom need for more than the appreciation of an experienced radiologist's eye. Furthermore, an enlarged heart is not always diagnostic of CHF. This is particularly true in the presence of valvular heart disease, for example aortic insufficiency.

Changes in the pulmonary circulation better reflect the condition of the left ventricle. Chest films are usually taken in the upright position. Normally pulmonary blood flow in upright position is greatest through the basal parts of the lungs. The width of the lung vessels reflects blood flow. Therefore the vessels are wide basally and very narrow in the apical parts. This distribution of pulmonary blood flow is governed by the influence of gravity, respiratory phase, total blood flow through the lungs and lung vein pressure.

The influence of gravity is quite obvious if the position of the patient is changed from upright to supine. The narrow vessels in the apical parts of the lungs in upright position dilate and the vessels in all parts of the lungs appear of about the same width (Figure 1a and 1b (next page)). Therefore supine chest films whether taken in the wards or in the x ray department lend themselves very poorly to the detection of changes in the pulmonary circulation.

The phase of respiration is also of great importance. The lung vessels may be divided into alveolar and extraalveolar interstitial vessels. The interstitium contains the artery and vein while the alveolar walls contain the capillaries. In the expiratory phase the interstitial space is small and the artery and vein therefore small. During inspiration the interstitial space is larger and thereby the artery and vein are distended while the capillaries moreover are compressed. Thus during inspiration the vessels in the parts of the lungs which are best ventilated, i.e. the basal parts, dilate while in expiration the vessels in the basal parts get narrower. Blood flow is diverted to apical parts of the lung and the difference in width between the parts is diminished.

In the pulmonary circulation a low pressure is needed to force the blood through the capillary bed. There is moreover a large resource of capillaries which can be recruited if there is a demand for higher flow through the lungs arise. The pulmonary artery pressure therefore still may be maintained at a low level. Demand for increased pulmonary blood flow arises for example during exercise or during pregnancy but is also evident in the presence of an intracardiac shunt. At chest films the lung vessels then may be seen to dilate. The pattern of dilatation is uniform but since the basal vessels initially are more dilated the dilation is easier to perceive in the middle or even apical lung fields. The difference in width between apical and basal parts of the lungs diminishes or may even disappear (Figure 2). The effect of overhydration is similar.

The pressure gradient between the pulmonary artery and vein in the basal parts of the lung is normally constant. This pressure gradient is balanced by the colloid osmotic pressure of blood and the surface tension in the alveolae and only a small amount of fluid passes through the capillary wall and can be carried away by the lymphatics. In CHF the end-diastolic pressure of the left ventricle and thereby also the pulmonary venous pressure is increased. This increase causes an increased amount of fluid to enter the interstitial tissue space. Following this the extraalveolar vessels cannot expand properly since they are isolated

From the Department of Diagnostic Radiology, University Hospital, Lund, Sweden

RADIOLOGICAL DIAGNOSIS

Ulf Tylén

The radiological diagnosis of congestive heart failure (CHF) is based on changes in the size of the heart and of the pulmonary circulation.

Enlargement of the heart is usually quite easy to recognize. Although there are elaborate methods for calculation of the size these methods have many sources of error and generally there is seldom need for more than the appreciation of an experienced radiologist's eye. Furthermore, an enlarged heart is not always diagnostic of CHF. This is particularly true in the presence of valvular heart disease, for example aortic insufficiency.

Changes in the pulmonary circulation better reflect the condition of the left ventricle. Chest films are usually taken in the upright position. Normally pulmonary blood flow in upright position is greatest through the basal parts of the lungs. The width of the lung vessels reflects blood flow. Therefore the vessels are wide basally and very narrow in the apical parts. This distribution of pulmonary blood flow is governed by the influence of gravity, respiratory phase, total blood flow through the lungs and lung vein pressure.

The influence of gravity is quite obvious if the position of the patient is changed from upright to supine. The narrow vessels in the apical parts of the lungs in upright position dilate and the vessels in all parts of the lungs appear of about the same width (Figure 1a and b) (next page). Therefore supine chest films whether taken in the wards or in the x-ray department lend themselves very poorly to the detection of changes in the pulmonary circulation.

The phase of respiration is also of great importance. The lung vessels may be divided into alveolar and extraalveolar – interstitial vessels. The interstitium contains the artery and vein while the alveolar walls contain the capillaries. In the expiratory phase, the interstitial space is small and the artery and vein therefore small. During inspiration the interstitial space is larger and thereby the artery and vein are distended while the capillaries moreover are compressed. Thus during inspiration the vessels in the parts of the lungs which are best ventilated, i.e., the basal parts, dilate while in expiration the vessels in the basal parts get narrower, blood flow is diverted to apical parts of the lung and the difference in width between the parts is diminished.

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Figure 4 a) Normal distribution of pulmonary blood flow in 63-year old male

b) Two years later atrial fibrillation. Redistribution of pulmonary blood flow

from the normally low interstitial pressure. The vessels therefore tend to collapse and blood flow is reduced. The oedema in the extravascular space moreover causes a decrease in the compliance of the lung which cannot be properly ventilated. As a result of these processes blood flow through the basal parts of the lungs cannot be maintained. Blood flow is therefore deviated to more cranial parts – redistribution occurs. There is a good correlation between the extent of redistribution and the pulmonary venous pressure (Figure 3). This has been demonstrated in mitral stenosis. The changes, however, are as obvious in left ventricular failure or obstruction to lung vein blood flow of any kind (Figure 4).

The redistribution of blood flow is a very sensitive indication of increase in pulmonary venous pressure. It starts already at pressures around 15 mm Hg. At a slightly higher pressure level (20–23 mm Hg) the oedema in the interstitial space may be demonstrated on chest films. There is thickening of the interlobular septae basally and due to the oedema around the vessels these appear unsharp. At pressures above 25 mm Hg alveolar oedema may be seen, to begin with as small patchy areas of increased density but gradually with increased oedema the lung gets a more or less uniform high density, the fulminant pulmonary oedema. In the meantime also fluid in the pleural cavities appear.

All these changes are quite characteristic and if marked, easy to detect. Since the development of the changes is a gradual process, the early detection of for example redistribution may be very difficult unless there is an old film at hand by means of which differences may be demonstrated.

Redistribution may be caused also by primary lung parenchymal disease. Fibrosis as well as obstructive lung disease causes blood flow to be diverted away from diseased areas. The presence of lung disease is usually well known but nevertheless differential diagnostic difficulties arise when there is question of CHF in such a patient.

continued next page

Figure 1 a. Normal distribution of blood flow in upright position. Vessels in upper part of the lung narrower than those of the lower

Figure 1 b. Same patient examined few minutes later in supine position. Redistribution of blood flow. Vessels in upper and lower parts of the lung have the same width.

Figure 2. Chest film in upright posit in a patient with atrial septal defe Vessels in upper as well as lower pa of the lung wider than normal

Figure 3. Distribution of pulmonary blood flow at varying lung vein pressure

a) PVC 18 cm H_2O. Light redistribution with vessels in upper parts of the lung wider than normal.

b) PVC 22 H_2O. Marked redistribution of blood flow from lower to upper parts of the lung. Early edema in the basal lung parenchyma.

c) PCV 44 cm H_2O. Marked redistribution. Marked interstitial edema basally.

scope is the best tool for detecting pulmonary congestion and this is probably true in most cases. However now and then, there are patients in the intensive care units with marked signs of pulmonary congestion on the chest X ray without any obvious findings at physical examination. Is that another kind of CHF which is not possible to detect with the stethoscope

Wallentin.

We have to differentiate between interstitial and alveolar edema of the lungs I do not think that any clinician can hear the rales of interstitial edema which is an early phase of CHF It can however be seen on the X-ray picture at least in some instances Many years ago I looked on pulmonary mechanics in patients with slight CHF Nothing could be heard at the lung examination, but a slight increase of the interstitial fluid was seen. There was a rather marked increase of the airway resistance of the lungs, but not any significant decrease of compliance One or two days of diuretic therapy improved the X-ray picture and the airway resistance markedly and there was a decrease of body weight by two kg Thus, I do think that we may get some information from pulmonary X ray in early stages of CHF Probably not as much from bedside ones of questionable technical quality but from examinations in the standing or sitting position

CONCLUSION

Changes in the pulmonary circulation are better correlated to CHF than is a change of heart size or shape. Redistribution of blood flow from basal to apical parts of the lungs is the most sensitive sign Redistribution cannot be detected on supine films.

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DISCUSSION

Pleural effusion

Johansson

An additional feature of the radiological diagnosis of CHF is pleural effusion which sometimes develops very rapidly for example in patients with an AMI. It is said that there is a predominance for the right side. If this is true why?

Tylén.

I do not know

Johansson

It might be that these patients sleep on their right side and due to the force of gravity transudate accumulates in the right pleural space. Vanishing tumors or phantom tumors in the lung due to a localized edema is sometimes an expression of CHF How often do you see these?

Tylén

If you with a vanishing tumor mean a localized encapsulated pleural effusion it is quite often found Its appearance and localization dorsally or in the interlobar fissures is typical. Since often however only frontal projection is used at bedside examination the recognition may sometimes be difficult

Bedside chest X ray

Berlin

Is it completely useless to utilize bedside chest X ray with the patient in the supine position in an acute situation to evaluate CHF? It seems to be used quite often in our country

Tylén

The information provided by a bedside examination is far from that of an examination in upright position A crude evaluation may however be made although I think it is a very unreliable examination in the diagnosis of early CHF

Holmgren

Why then is bedside chest X ray used with such great success in intensive care units after open heart surgery? Can you give us an explanation? What you are saying is that it is not possible to estimate the level of the pulmonary arterial pressure on these chest X rays but still there is a lot of other information to be obtained from a bedside picture.

Tylén.

CHF may often be diagnosed by physical examination of the patient. After surgery however this evaluation is more difficult Postoperative bedside examination therefore may be worthwhile Particularly since so many other factors may be checked for example the presence of pneumothorax or atelectases My point however is that too much weight should not be put into bedside chest examination in the recumbent position An effort should at least be made to investigate the patient sitting up

Persson

I think we might be talking about different pulmonary manifestations of CHF Tylen tells us that the steth

scope is the best tool for detecting pulmonary congestion and this is probably true in most cases. However now and then, there are patients in the intensive care units with marked signs of pulmonary congestion on the chest X-ray without any obvious findings at physical examination. Is that another kind of CHF which is not possible to detect with the stethoscope.

H. [illegible]

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NON INVASIVE METHODS FOR ASSESSING CARDIAC PERFORMANCE IN CHF

John Wikstrand and Ingemar Wallentin*

INTRODUCTION

In the early 70s pressure curves derived from the left ventricle with tip manometers and the first derivative of the pressure signal during the isovolumic contraction phase aroused great interest. Such variables as dp/dt, dp/dt/P and above all V_{max} were thought by many cardiologists to be the key to the judgement of left ventricular pump function. Although the method was very sophisticated, complicated and invasive, it did not give what it promised (Peterson *et al.* 1974, [illegible] *et al.* 1975). The explanation is, among other things, that no single method, however sophisticated, invasive and complicated it may be, can give enough information about cardiac performance to enable the correct diagnosis to be established.

This is not surprising since the pump is a very complicated structure. We need information about several variables to be able to diagnose cardiac dysfunction and congestive heart failure (CHF) correctly. Among the major variables of interest are the left ventricular filling pressure, pulmonary artery pressure, left ventricular volume, wall thickness, and systolic function, arterial blood pressure and flow and mitral and tricuspidal valve function (Figure 1).

A combination of non-invasive investigations can give a great deal of information about these variables and thus create a good foundation for a correct diagnosis of pump function in CHF and thus also for the choice of therapy. The aim of this paper is to give a brief review of the most important non-invasive me-

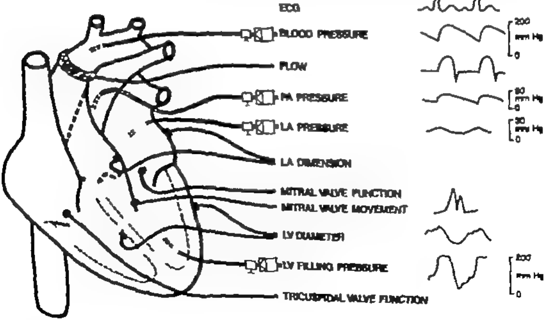

Figure 1. Schematic presentation of the variables of interest when diagnosing cardiac dysfunction.

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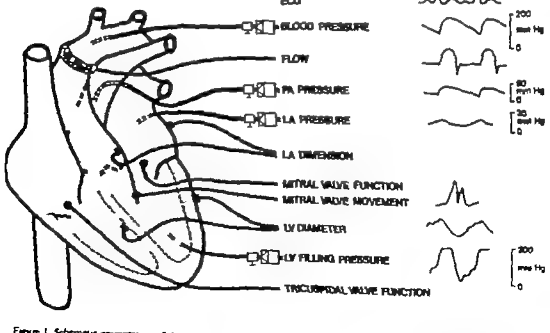

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LEFT VENTRICULAR DIASTOLIC FUNCTION AND FILLING PRESSURE

Several non invasive methods are needed for judgement of filling pressure and diastolic function of the left ventricle. Among these are also methods reflecting the relationship between left ventricular filling pressure and left ventricular volume, that is to say the distensibility or compliance of the left ventricle. Furthermore, variables mirroring pulmonary artery pressure are needed.

Third and fourth heart sound and the diastolic part of the apex cardiogram

The relationship between diastolic volume and left ventricular filling pressure defines distensibility (Figure 2). Distensibility early in diastole can be judged from the 3rd heart sound and from the rapid filling wave in the apex cardiogram and distensibility during the atrial contraction can be judged from the 4th heart sound and from the a wave in the apex cardiogram. The 3rd and 4th heart sounds recorded phonocardiographically are very important and sensitive indices of disturbed left ventricular function. The diastolic

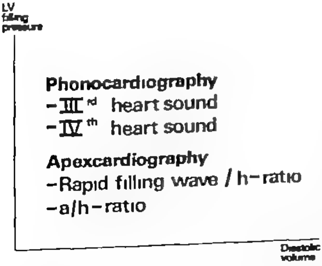

Figure 2 The relationship between diastolic volume and left ventricular filling pressure defines distensibility which can be judged non-invasively by phonocardiography and apex cardiography

extra sounds, when recorded phonocardiographically can be normalized with the amplitude of the 1st heart sound, and the rapid filling wave and the atrial wave in the apex cardiogram can be normalized with the total height of the apex curve (Gibson *et al.* 1974 Waagstein *et al* 1975 Wikstrand 1976 Swedberg *et al* 1980^a, b^ Vedin *et al* 1980).

A major problem in evaluating the gallop sounds and the diastolic part of the apex curve is that these recordings probably reflect cardiovascular functional characteristics that are not measured by conventionally employed haemodynamic parameters in man. This is probably the reason why the gallop sounds and the diastolic part of the apex curve, old techniques, have not as yet been generally accepted as a valuable means of assessing left ventricular diastolic function.

It is, however becoming apparent that the diastolic events, particularly those associated with relaxation and filling of the ventricle, are major determinants of the overall function of the left ventricle. Non-invasive techniques appear to be the methods of choice for studying them

Computer processing of dimensional changes during diastole

It is possible that computer processing of echocardiographic recordings of dimensional changes of the left ventricle throughout the cardiac cycle will become a valuable tool for diagnosing disturbances of left ventricular diastolic function The position of the endocardium can be recorded continuously in terms of a set of coordinates, stored by computer This makes it possible to derive plots of the left ventricular dimension continuously throughout the cardiac cycle along with its first derivative so that the peak rates of dimensional changes during systole, relaxation and filling of the left ventricle can be derived

Several groups are working on this problem and Gibson s group in London has made important contributions in this field (Gibson 1978) The apex cardiogram and left ventricular echocardiogram are recorded simultaneously and the apex cardiogram and the left ventricular diameter are later digitized and left ventricular function curves processed (Figure 3 next page)

Figure 4 shows a similar recording from Hanrath s

group in Hamburg (Hanrath *et al.* 1980). Time is shown on the horizontal axis and on the vertical axis the lower curve shows the dimension of the left ventricle measured by echocardiography and the upper curve the first derivative of these dimensional changes throughout the cardiac cycle. The first derivative of the left ventricular dimension changes – the upper curve – shows a pronounced deflection in connection with ejection, during the rapid filling phase and during atrial contraction. It is to be hoped that these types of recordings will lead to an increased theoretical understanding and more reliable diagnosis of important functional disturbances during left ventricular relaxation and filling.

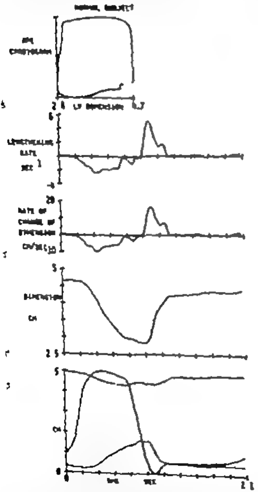

Figure 3 Digitized echocardiogram from normal subject. Plots represent, from below digitized data, left ventricular dimension, rate of change of dimension in cm/sec, rate of change of dimension, normalized (VCF), and top, the relations between apexcardiogram and dimension, used for the detection of incoordinate contraction or relaxation (from Gibson 1978).

Echocardiographic recording of mitral valve movements

Figure 5 (next page) presents a schematic illustration of different types of mitral valve movement at different filling pressures in the left ventricle (Konecke *et al.* 1973). The left panel (A) shows normal left ven-

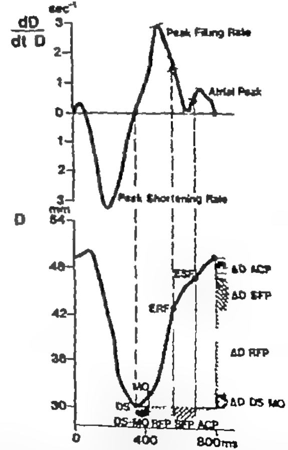

Figure 4 Dimension-time curve and its first normalized derivative for analyses of the different phases of left ventricular filling. ACP = filling phase due to atrial contraction; D = dimension, DS = end-systolic dimension, ERF = end-point of the rapid filling phase, ESF = end-point of the slow filling phase; MO = mitral valve opening, RFP = rapid filling phase; SFP = slow filling phase; t = time (from Hanrath *et al.* 1980).

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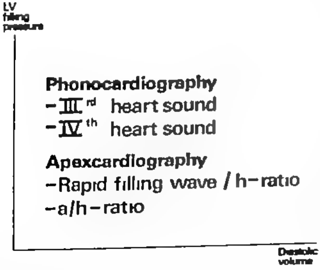

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monary hypertension, as shown in Figure 8 (next page), published by Weyman and co-workers (Weyman *et al.* 1974). The upper panel (A) shows a normal pattern with a pronounced a-wave during atrial contraction and not too rapid opening of the leaflet in early systole. In pulmonary hypertension, on the other hand, the a-wave decreases in amplitude and the opening in early systole is more rapid, as illustrated in the lower panel (B). The authors have pointed out, however, that the movement pattern must of course be judged with caution if the filling pressure in the right ventricle is increased. Right ventricular systolic time intervals have also been used to predict pulmonary artery pressure (Fernandes *et al.* 1980).

LEFT VENTRICULAR SIZE, SYSTOLIC PUMP FUNCTION AND FLOW

With echocardiography it is possible to measure left ventricular size and wall thickness. Flow is a more complicated problem.

Table I. Correlation coefficients for two-dimensional and unidimensional derived volumes as compared to left ventricular cineangiographic volumes

	End diastolic volume	End systolic volume	All volumes
Modified Simpson rule (two dimensional)	0.82 (39)	0.90 (29)	0.87 (39)
Unidimensional left ventricular internal dimension*	0.72 (47)	0.81 (39)	0.79 (49)

Standard error of the estimate (in cc) are in parentheses
*Using modified ellipsoid formula.

Left ventricular size

Table I shows correlation coefficients for two-dimensional and unidimensionally derived left ventricular volumes as compared with angiographic volumes reported by Parisi and co-workers at a symposium on

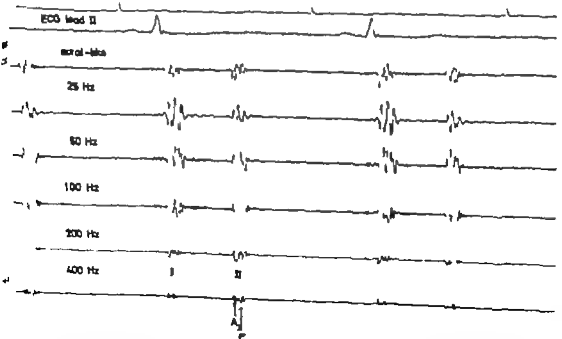

Figure 7. Phonocardiogram from the left second intercostal space paradoxically showing an augmented pulmonary component (P_2) of the second heart sound, from a patient with decreased left ventricular function after myocardial infarction

tricular filling pressure and a normal mitral valve movement. Panel B illustrates normal filling pressure before atrial contraction but an increased filling pressure during atrial contraction. In this case there is a prominent notch in the movement pattern of the mitral valve after the atrial contraction and before the start of systole which is not seen in the normal recording. The right panel (C) illustrates increased left ventricular diastolic filling pressure already *early* in diastole. In this case the mitral valve shows a decreased rate of closure after maximal opening during early diastole, with a pronounced a wave during atrial contraction. *Further studies are needed to document this* quantitative approach to predicting left ventricular filling pressure from timing and movement of the mitral valve. In our experience, as in that of several other groups, these types of pathological mitral valve movements are almost always seen in patients who also present other signs of disturbed diastolic or systolic left ventricular function (Layton *et al* 1973).

Left atrial size

Left atrial enlargement mirrors the longstanding increase in left ventricular filling pressure and Figure 6 shows on the horizontal axis the left atrial size as judged by angiography and on the vertical axis the left atrial dimension as measured by echocardiography. Several groups have reported similar close correlations between measurements of left atrial dimension on angiography and echocardiography (ten Cate *et al.* 197… Recording of left atrial size by echocardiography i… thus well validated and left atrial size is an importa… part in the puzzle of correctly diagnosing left ve… tricular dysfunction.

PULMONARY ARTERY PRESSURE

Marked increases in left ventricular filling pressu… early in diastole may lead to pulmonary hypertensio… of secondary origin. Another part in the puzzle of le… ventricular function thus concerns the diagnosis o… *pulmonary hypertension.*

Pulmonary component of the second heart sound

One index of increased pulmonary artery pressure i… an increased amplitude or a higher frequency of the pulmonary component in the 2nd heart sound, as il… lustrated in Figure 7 (next page). High quality pho… nocardiograms free from noise are a prerequisite fo… correct evaluation.

Echocardiographic recording of the pulmonary valve

The movement pattern of the pulmonary leaflet a… recorded by echocardiography might also indicate pul…

Figure 5 Schematic diagram of the three different types of mitral valve movement. Also included are simulated simultaneous left ventricular (LV) and left atrial (LA) pressures and the ECG. See text for discussion (from Konecke *et al* 1973).

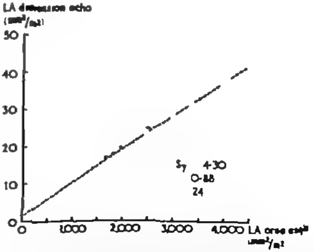

Figure 6 Correlation between the echocardiographic left atrial dimension and left atrial area as determined by cineangiography. Both values for left atrial size are corrected for body surface area. The broken lines represent the calculated regression lines and the stippled area the standard error of the estimate (Sy.x) (from ten Cate *et al* 1974).

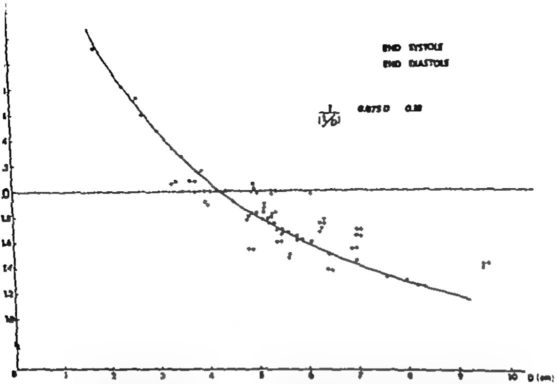

Figure 9 Relation between the ratio of the long to the minor axis (L/D ratio) and calculated minor axis D obtained from right anterior oblique angiograms D_{RAO}. The dotted line represents an L/D ratio of 2. The open circles indicate end-systolic and the closed circles end-diastolic data. The points fit a single hyperbolic equation (from Teichholz *et al.* 1976).

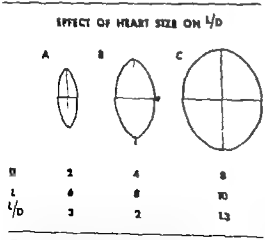

Figure 10 Effect of heart size on the ratio of the long to the minor axis (L/D ratio). A represents a small heart, B a "normal" sized heart and C an enlarged heart (from Teichholz *et al.* 1976).

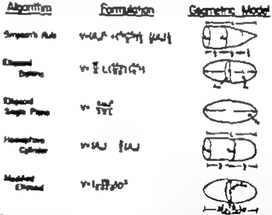

Figure 11 Summary of the geometric models and algorithms used to generate left ventricular volume and ejection fraction from two-dimensional echo data. A = area measurements, L = the longest length of the ventricle from the longaxis section, D = the septal-lateral diameter from the high cross-section of the ventricle. The subscripts m, p, and 1 refer to the mitral valve, papillary muscle, and long-axis sections, respectively (from Folland *et al.* 1979).

non invasive cardiac diagnosis 1980 The upper line represents values for two-dimensional echocardiography against angiography and the lower line unidimensional M mode derived volumes correlated with angiographic volume. It will be seen that there is a good correlation for two-dimensional and a rather good correlation also for unidimensional volumes

Similar figures have been presented by other groups and when patients with asymmetric contractions are excluded from the unidimensional calculations the correlation coefficients become slightly higher (Pas *et al* 1980). Some investigators prefer to confine estimates of ventricular function by the M-mode method to measurement of the changes in minor axis of the left ventricle alone without extrapolation to determinations of volume, but this is more or less a matter of taste.

Deviations from correct volume determinations are commonly encountered in large ventricles, which tend to become spherical (Figure 9 and 10 next page) (Teichholz *et al* 1976). Other deviations can be explained by aneurysmal bulges or segmental contraction abnormalities, which can distort the ventricle in systole. It is generally understood that the reliability of volume determinations by M mode echocardiography depends on the absence of segmental contraction abnormalities Although M mode echo-internal dimensions and two-dimensional echo-cross-sectional areas vary consistently with ventricular size, they appear to be a reliable *index* of ventricular volume. More accurate prediction of ventricular volume and output by echocardiography requires further evaluation and refinement of the echocardiographic instrumentation, examination techniques and data processing procedures. Several geometrical methods have been proposed in order to improve estimates of left ventricular volume (Figure 11 next page) (Folland *et al* 1979).

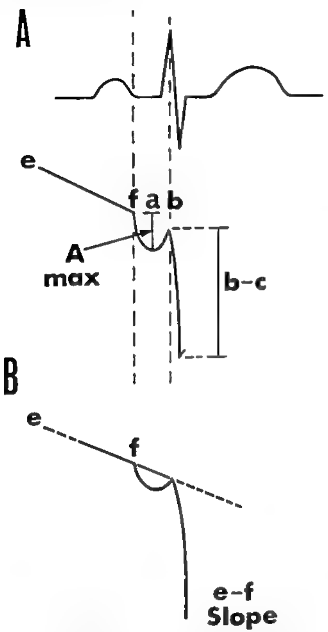

Figure 8. Diagram demonstrating various motion patterns of the pulmonary leaflet. A. A Max = maximum depth of the a wave measured during the inspiratory phase of quiet respiration b-c opening = amplitude of systolic opening of the posterior leaflet B e f slope = measurement from the maximum anterior point of the posterior leaflet to point f the position of the leaflet at the onset of atrial systole. In normal subjects, at slow heart rates (< 70/min), the e-f slope will frequently end before atrial contraction occurs In these cases a short usually flat segment is interposed between point f and the onset of the a wave. The length of this segment is directly related to the cycle length In this situation, the initial rapid slope was measured (from Weyman *et al* 1974)

Indices of ejection phase function left ventricular ejection fraction and mean V_{CF}

Several studies have been performed to validate echocardiographically derived ejection fraction measurements with those derived from left ventricular angiograms. Figure 12 presents a correlation analysis from our own laboratory at Sahlgrenska Hospital Gothenburg, Sweden The analysis was performed in three groups of patients, one with congestive cardiomyopathy and two angina pectoris groups one with negative and one with positive coronary angiographi

however are only a small part of the whole puzzle of left ventricular function (Wikstrand *et al* 1978) Their popularity reflects how easy they are to record rather than the information they contain. However a shortened left ventricular ejection time, as in Figure 13 (80 % of the expected value for the given heart rate), is an indication of low *output*, and a very low left ventricular ejection time, down to 60–70 % of the expected value at a given heart rate, is a very poor prognostic sign, only seen in patients with very low output.

Impedance cardiography

There has always been a high level of interest in non-invasive determinations of SV and CO. This problem is a difficult one. It has been claimed that impedance cardiography is a reliable non-invasive method for assessing CO. Figure 14 shows a recording from our laboratory from the top, an impedance cardiogram with its first derivative, followed by chest ECG leads and, at the bottom, the carotid pulse tracing recorded in our laboratory. All curves were recorded during heavy exercise, stored and averaged by computer resulting in a high quality impedance cardiogram with its first derivative, chest ECG leads and a carotid pulse tracing, free from noise and baseline deviations (Angelhed *et al* 1978). In contrast to echocardiography this method can be recorded relatively simply during exercise. A major problem in evaluating the impedance cardiogram as a meaningful expression of CO however is the fact that the impedance cardiogram probably reflects cardiovascular characteristics that are not measured by conventionally employed methods in man. Impedance cardiography conveys information which is fundamentally different from CO. Impedance cardiography both at rest and during exercise, requires further documentation to evaluate further documentation to evaluate its physiological significance and its usefulness in the diagnosis of cardiac dysfunction.

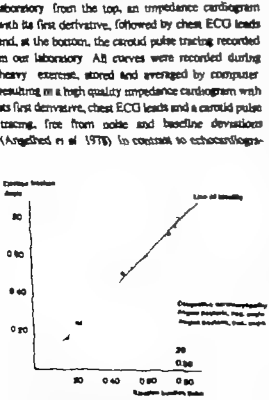

Figure 12 Correlation analysis between ejection fraction derived from biplane angiography and M-mode echocardiography respectively in three groups of patients with a wide range of ejection fraction values (See text for discussion)

LEFT VENTRICULAR WALL THICKNESS

If we are to establish the correct diagnosis in CHF we have to define distensibility contractility and output in the light of the morphology. That is why it is important not only to measure the left ventricular internal diameter in the echocardiogram but also to measure wall thickness. Wall thickness is a very important variable since hypertrophy is a common finding in patients presenting symptoms typical of CHF. These patients probably benefit from therapeutic interventions fundamentally different from what those with poor systolic pump function require (Vedin *et al* 1980).

This is probably not a minor problem since hypertension and ischaemic heart disease, main determinants of wall thickness and distensibility are prominent features in the epidemiology of CHF. In these patients high filling pressures with severe symptoms indicating heart failure can often be seen in spite of a perfect systolic contraction. (Wikstrand *et al* 1978 Vedin *et al*. 1980).

MITRAL AND TRICUSPIDAL REGURGITATION OF SECONDARY ORIGIN

The occurrence of mitral regurgitation and tricuspidal regurgitation is important to judge. It is also of fundamental importance to be able to evaluate changes in ejection fraction or mean V_{CF} in the relation to changes in mitral regurgitation. Deterioration in left ventricular function with an increase in mitral regurgitation can lead to an increase in ejection fraction,

The analysis gave an r value of 0 96 One patient deviates considerably from the identity line, with an ejection fraction of 0 57 at left ventricular angiography and 0 78 at echo This patient was the only one in the angina pectoris group with a pathological Q-w in the Minnesota coded ECG (Rose & Blackburn 19 He had no history of clinical myocardial inf however

Table II Relationship of echocardiographic to angiocardiographic ejection fractions.

Reference	Method	N	r	SEE	Comments
M mode studies					
Pombo *et al*	Cube formula	27	0 80	0 09	Mixed patient group (13/27 VHD 3/27 IHD
Fortuin *et al*	% ΔD	27	0 79	0 07	Mixed patient group (19/27 VHD 1/27 IHD
Quinones *et al*	Regression formula	42	0 90	0.08	Patients selected to have no detectable asynergy
Teichholz *et al*	Modified ellipsoid formula	11	0 79	-	Patients without asynergy
		14	0.37	-	Patients with asynergy
Two-dimensional studies					
Teichholz *et al*	B scan	25	0 87	-	14/25 had asynergy
Folland *et al*	Modified Simpson s rule	70	0 85	0 07	
Parisi *et al*	Modified Simpson s rule	50	0.80	0 09	25/50 had asynergy
		25	0 83	0 08	25 patients only with asynergy
Carr *et al*		22	0.93	-	6/22 had asynergy
Schiller *et al*		14	0 92	0 06	9/14 had asynergy
Chaudry *et al*	3 axis measurement	30	0 73	-	20/30 had IHD
Nixon *et al*		9	0 79	0 04	

N= number of patients; r= linear correlation coefficient, SEE= standard error of the estimate; VHD= valvular heart disea IHD= ischemic heart disease

Table II shows the relationship between echocardiographic and angiographic ejection fraction in a series of studies (Parisi *et al* 1980). The upper part concerns unidimensional comparisons with angio and the lower part two-dimensional echocardiographic determinations and comparisons with angiography It will be seen that there is a good correlation with two-dimensional echocardiography even in patients with asymmetric contraction, which is not the case with M mode single beam determinations. In similar studies mean V_{CF} values determined echocardiographically and angiocardiographically have also correlated reasonably well (Cooper *et al* 1972, Quinones *et al* 1974). Thus, once more determination of both volume and indices of the left ventricular ejection phase, such as ejection fraction and mean V_{CF} depends on the absence of segmental contraction abnormalities when only M mode echocardiography is used Two-dimensional echocardiography eliminates many of the limitations of M mode echocardiography When both techniques are used together however the results a extremely complimentary for the assessment of car iac anatomy and function since M mode offers a tim motion display and also better identification of cardi structures delineating wall thickness. It is importa to appreciate that echocardiographic techniques a fundamentally limited by the quality of sound tran mission characteristics in a given patient Images a impaired by chronic lung disease, abnormal chest wa configuration and high patient age, among other fa tors. Cross-sectional two-dimensional echocardiogra phy is superior to M mode in this respect since echoe can in most cases be derived from the apex or fro the subcostal view

Systolic time intervals

Figure 13 shows a simultaneous recording of the ECG the phonocardiogram and the carotid pulse tracing From these simultaneous recordings the systolic tim intervals can be derived. The systolic time intervals

which can falsely be interpreted as an improvement in LV function. Institution of therapy, for example vasodilation, can on the other hand lead to a decrease in ejection fraction secondary to a decrease in mitral regurgitation, although the overall LV function has improved considerably.

Mitral regurgitation

In mitral regurgitation the regurgitant volume is not always well correlated to the intensity of the regurgitant murmur. That is one reason for the growing interest in Doppler techniques in this field. The sensitivity and specificity for detection of mitral regurgitation has been assessed by means of a range-gated Doppler by Abbasi *et al.* In a paper presented in Circulation (Abbasi 1980). Figure 15 shows on the horizontal axis the doppler estimate of mitral regurgitation according to standardized procedure and on the vertical axis the angio estimate. The degree of mitral regurgitation estimated with the Doppler technique was shown to be highly correlated with that determined by angiography.

Tricuspidal regurgitation

With progressing disease, tricuspidal regurgitation may develop. This can easily be diagnosed non-invasively with venous pulse tracings as illustrated in

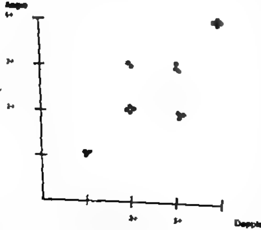

Figure 15. Comparison of left ventriculographic (Angio) and Doppler estimation of the degree of mitral regurgitation (from Abbasi *et al.* 1980).

Figure 16, which shows a jugular venous tracing and a hepatic tracing, both with prominent, positive systolic s-waves in systole, where the curves should have been downward sloping. These prominent s-waves indicate tricuspidal regurgitation of clinical significance.

Further documentation of tricuspidal regurgitation can be achieved by two-dimensional echocardiography. With the apex view and contrast saline injections in the antecubital vein, images are obtained that are similar to those obtained by right-sided angiography but with the advantage that no catheter is passed between the right atrium and right ventricle and no contrast medium is present to precipitate arrhythmias. In cases of tricuspidal regurgitation contrast is seen circulating between the right ventricle and right atrium and also during each systole down into the inferior vena cava and portal vein. Doppler can also be used to detect tricuspidal regurgitation.

ADVANTAGES AND DISADVANTAGES OF NON-INVASIVE CARDIAC INVESTIGATIONS

It is clear from this review that non-invasive investigation of cardiac function is not simple and rapid but complex and time-consuming. The obvious therapeutic advantage of being able to determine the correct cardiac diagnosis without cardiac catheterization should, however, lead to lower costs of hospitalization and eliminate the cost and risk of diagnostic cardiac catheterization in many cases. As with all methods, the reliability and value of the results are directly proportional to the technical quality of the recordings from which they are derived and to the experience of the investigator.

Interpretation of the non-invasive investigation calls for extensive experience of the methods and a profound knowledge of cardiology. The interpretation is based on a synthesis of the phonocardiogram, pulse curves, apex cardiogram, echocardiogram and Doppler. In most cases the findings show a pattern that gives a good foundation for correct diagnosis. If the findings for some reason do not fit together to form a pattern the diagnosis should be reconsidered. When the non-invasive methods are used in combination in the way suggested they usually lead to a correct diagnosis as regards both type and severity of cardiac dysfunction, often giving more information than can

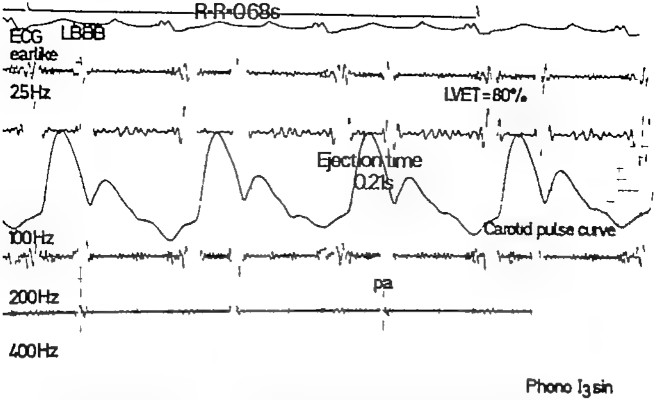

Figure 13 Carotid pulse tracing from a patient with CHF and LVET decreased to 80 % of the expected value at given heart rate Note that the components of the second heart sound are reversed due to left bundle branch block (LBBB) (p = pulmonary component a = aortic component of the second heart sound). (See text for discussion.)

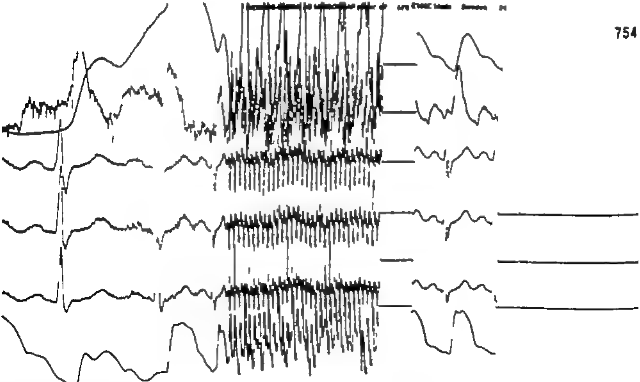

Figure 14 Recording of, from top to bottom: Impedance cardiogram with its first derivative, chest ECG leads CH_2, CH_4, CH_5 and carotid pulse tracing during heavy exercise on an ergometer bicycle Sampling period to the left and m curves to the right (See text for discussion.)

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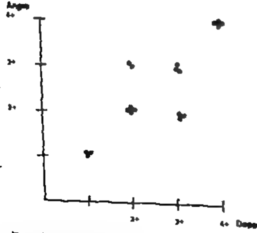

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be achieved with the more conventional invasive methods – cardiac catheterization with pressure recordings and contrast investigation – and with considerably less discomfort and risk to the patient and lower cost to the health service.

As regards the future, we have to define the variables that are of fundamental importance for judgement of the prognosis and the progress of the pump function and the patient and also the variables that are of essential importance for judgement of the need for and type of therapeutic intervention. Some patients with CHF may benefit from digoxin or thiazides, others from beta-blockers still others from beta-stimulants or vasodilators or different combinations of these drugs. Non invasive methods are the metho of choice for assessing the morphology and functio of the pump, which is of fundamental importance f a correct choice of therapy.

What haemodynamic changes reflect improveme in quality of life or an improved prognosis or bot It is not enough to measure a higher CO or a hig ejection fraction or to note the disappearance of a m tral regurgitation. Therapeutic interventions have t be repaid by an improved quality of life or an improve prognosis or both. It is with this background that w have to define which therapy is of clinical value i different subgroups of patients with CHF.

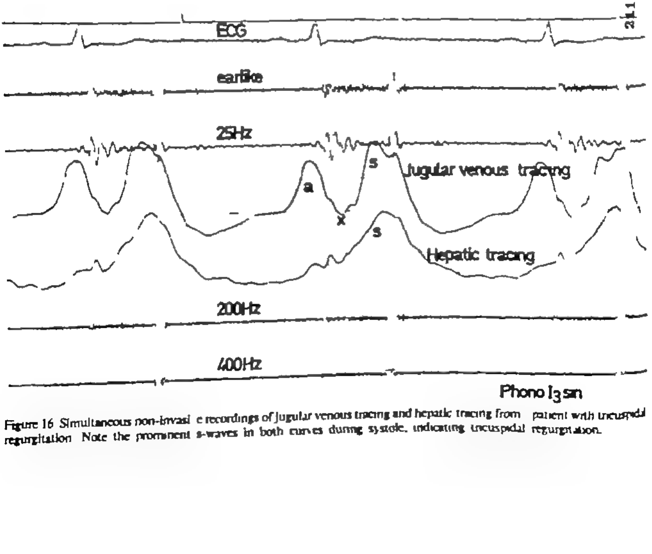

Figure 16. Simultaneous non-invasive recordings of jugular venous tracing and hepatic tracing from patient with tricuspidal regurgitation. Note the prominent s-waves in both curves during systole, indicating tricuspidal regurgitation.

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CO_2 rebreathing for determination of CO

Swedberg

There are few non invasive methods for the estimation of CO However one method that has not been discussed is the CO_2 rebreathing used by Dr Cohn I would like a critical discussion of that method

Cohn

I believe it is a useful technique and to my knowledge the only one giving more exact values during exercise than rest The problem with the method primarily relates to minor discrepances in using expired gas as an assessment of mixed venous and arterial blood oxygen content During exercise the hyperventilation makes the non-invasive measurement of blood gases more exact We have found the method quite reproducible. There are patients in whom absolute values of CO are not reliable. Unfortunately it is not always possible to detect the patient in whom this may occur due to gas exchange problems. I do not know the percentage of such patients. Nevertheless the method seems to be quite reliable for the detection of changes in CO as a result of interventions It is simple to carry out and we have been using it during five to six ye[illegible] It has been a valuable tool to add information to t[illegible] observations made on the patients.

Measurement of the thoracic impedance

Eliasch

Some physiologists claim that measurement of t[illegible] thoracic impendance is very useful for the evalua[illegible] of the degree of pulmonary congestion especially a[illegible] an intervention with a pharmaceutical agent. Do y[illegible] have any experience on that?

Wikstrand

I think it is one thing to claim that it is a good meth[illegible] and another to prove this scientifically I am not aw[illegible] of any good validation of impendance cardiograph[illegible] I think that at present there is a misuse of data fr[illegible] this method I have seen several slides at differ[illegible] meetings where CO have been marked on the vertic[illegible] axis when, in fact a measurement of thoracic im[illegible]pendance had been performed. I feel very sceptic[illegible] to this. Our data are not encouraging.

RADIONUCLIDE EVALUATION OF CHF

Jan Lessem

Until recently invasive diagnostic procedures such as ventriculography and coronary angiography were the only reliable methods to determine left ventricular function and the status of the coronary arteries. Trials have been made (Corya 1977, Heikkilä & Nieminen 1975, Heikkilä & Nieminen 1978) to use echocardiography as a non-invasive tool, but the success of this method has not yet been proven. Imaging devices, radionuclides and computors have recently been applied in search for a more accurate and less traumatic method to determine myocardial wall motion and cardiac hemodynamics (Ashburn *et al.* 1978, van Dyke *et al.* 1972, Rigo *et al.* 1974). These techniques have improved tremendously since Blumgart & Yens used them in 1927 or since Prinzmetal and co-workers earlier trials 1956. An improvement of the imaging devices have constantly taken place. At the same time the computer techniques have become more advanced and more reliable than earlier. Finally the usage of $^{99}Tc^{m}$-labelled red blood cells (Hegge *et al.* 1978, Lessem & Popescu 1980) have improved the image quality and the image procedure making equilibrium studies more attractive. Both the left and right ventricular hemodynamics can be studied this way (Schad 1976), although a higher degree of safety can be expected when the left ventricle is concerned. Studies can be performed at rest (Bodenheimer *et al.* 1980, Jengo *et al.* 1978) or at stress (Borer *et al.* 1979). These techniques have shown themselves to be *repeatable* and measurements of ejection fraction have correlated well with those found at the invasive investigation.

Left ventricular ejection fraction can be studied by one of two methods: first pass or gated equilibrium radionuclide angiography. The most commonly applied method is the *gated equilibrium study*, although historically the first passage method was developed and used earlier (Ashburn *et al.* 1973, Blumgart & Yens 1927). While the *first passage technique* due to its by definition short data acquisition period of about 30 seconds is advantageous when exercise intervention studies are planned, the gated equilibrium technique allows for repeated studies for example before and after pharmacological intervention. A clinical advantage with the first passage technique is to be found in patients with an acute myocardial infarction (AMI), where one can study the first passage with $^{99}Tc^{m}$ pyrophosphate and a couple of hours later the same injection can be used to determine the myocardial uptake pattern and maybe verify the infarction diagnoses (Stokely *et al.* 1976, Toburick *et al.* 1978). When the gated technique is applied the count accumulation is synchronized to the cardiac cycle by using the R-wave in the ECG as a synchronizer marker and from there divide the cardiac cycle into many frames (Qureshi *et al.* 1978, Strauss *et al.* 1977), from which the end systolic and end diastolic are used to calculate the left ventricular ejection fraction and to determine the ventricular wall motion. Usually the latter is derived from a motion picture of all the frames added together. Naturally problems in calculating the ejection fraction can arise when severe arrythmias such as atrial fibrillation are present (Marshall *et al.* 1978).

One of the major problems in determining the correct ejection fraction has been the calculation of the background activity and several approaches have been adhered to (Atkins *et al.* 1977, Marshall *et al.* 1977). A rather new clinically not totally available computer program *with* an automatic background correction and delineation of the left ventricular borders in systole and diastole (Figure 1), with a combination of correction in both time and space has recently been developed and introduced by Verba and co-workers (Verba *et al.* 1980). This program does also allow for a study of the onset of the mechanical systole pixel by

**From the Heart Section, Department of Medicine, Malmö General Hospital, Malmö, Sweden*

pixel Ejection fractions can thus be calculated for single segments very reliably and if wall motion abnormalities are present such as for example dyskinetic or akinetic areas these will show a negative ejection fraction when this method is used The program also allows for a calculation of stroke volume (SV).

Usually the ejection fraction and wall motion determinations have been applied to patients with coronary heart disease Studies on the haemodynamics of the myocardium in patients suffering from an AMI have been performed and (Reduto *et al* 1978 Geddes *et al* 1980 Shah *et al* 1980 Steele *et al* 1976), it has been shown that severe dyskinesia and a markedly decreased ejection fraction means a worsened prognosis during the acute phase of the disease. When the long term prognosis of a patient is considered a more thorough examination of the haemodynamic status seems to be warranted Even if the ejection fraction is found to be very low this does not necessarily mean that the patient needs to go into CHF A correlation seems to exist between prognosis ejection fraction and the relative cardiac volume. The greater the latter and the smaller ejection fraction the less are patients able to survive with as the cardiac output (CO) is a function of both these parameters, and will be compensated for by the large volume.

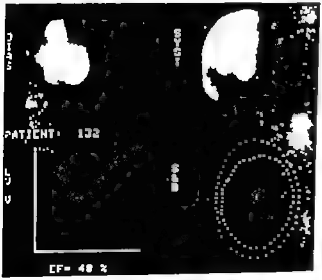

Figure 1 This figure demonstrates the end systolic and end diastolic frames after space and time correlation The bottom right picture shows the automatic search and contour delineation.

Other studies have been designed to detect ef infarction in patient populations (Schad 1977) Is isotope angiography has also been used to investi angina pectoris populations (Borer *et al* 1977 Je *et al* 1980) at exercise and rest to determine what ha pens to an ischemic myocardium. In this respect the studies have usually been combined with a ^{201}T perfusion study (Borer *et al* 1979 Bodenheimer *e* 1980) From these studies it can be concluded th the detection of abnormalities in left ventricular co traction at rest or during exercise is of great va in detecting and diagnosing coronary heart disease some of these abnormalities occured in patients w normal ECG.s (Upton *et al* 1979) or even before t pathological ST segments appeared (Berger *et al* 197

Recently these nuclear methods have been used determining pharmacological interventions in patie with coronary heart disease and drugs tested have be nitroglycerine (Salel *et al* 1976), beta blockers (Ma shall *et al* 1977) Ca ++ antagonists, prenal (Boström *et al* 1980) and vasodilators amongst othe The methods are ideally suited for these kinds of st dies as they repeatedly are inherent in at least th gated quilibrium method

Another area where these radionuclide techniqu have been very useful is in the diagnostics of CH be it due to ischemic heart disease, valvular dise or cardiomyopathy and in the evaluation of therapeu intervention with either vasodilators or digitalis

PATIENT POPULATION

Thirty two patients 30 males and 2 females, 40 t 72 years old with a mean of 60 2 years were all ex amined with the gated equilibrium technique us a scintillation camera (Maxi-camera – General Electr USA) and ECG-gate and a computer syste (PDP 11) All patients suffered from ischemic hea disease, but no one was examined during an acu phase of an infarction All the examinations were ca ried out ambulatory In all patients $^{99}Tc^{m}$ labelle red blood cells (Kabi Diagnostica, Sweden) was use All data were stored in the computer and the ejectio fraction calculations were done according to a self em ployed computer programme technique with a horse

shoe background area around the left ventricle without space but with time correction.

Two of the patients suffered from clinically verified CHF when examined. In five of the patients an intervention therapy was evaluated by repeating the gated study after administration of a drug. In one 5.0 ml of theofylline, in one 0.25 mg of digoxine, in one after 80 mg propranolol and 240 mg of verapamil and in the last two after 0.5 mg nitroglycerine had been administered sublingually.

No invasive investigations have been performed in this study group of patients.

Table 1. Number of patients for each tenth of the ejection fraction

EF	No. of patients
0.00–0.09	0
0.10–0.19	5
0.20–0.29	4
0.30–0.39	4
0.40–0.49	7
0.50–0.59	4
0.60–0.69	4
0.70–0.79	3
0.80–0.89	1

RESULTS

The ejection fraction calculated by the previously described method in this material varied between 0.10–0.82 (lower reference value of the laboratory 0.52), and Table 1 shows the result, exemplified in Figure 2. The lowest value 0.10 was found in a 56 year old male who had suffered a large and complicated anterior

Figure 2. A computer output scan showing the ejection fraction calculations in patient in the population. This patient had an ejection fraction of 14 %

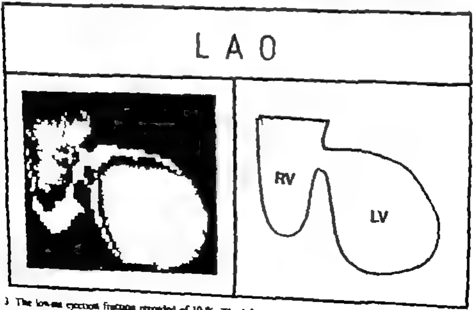

Figure 3. The lowest ejection fraction recorded of 10 %. The left ventricle is almost only an aneurysm which as also seen on the computed tomography

pixel Ejection fractions can thus be calculated for single segments very reliably and if wall motion abnormalities are present such as for example dyskinetic or akinetic areas these will show a negative ejection fraction when this method is used The program also allows for a calculation of stroke volume (SV).

Usually the ejection fraction and wall motion determinations have been applied to patients with coronary heart disease Studies on the haemodynamics of the myocardium in patients suffering from an AMI have been performed and (Reduto *et al* 1978 Geddes *et al* 1980 Shah *et al* 1980 Steele *et al* 1976) it has been shown that severe dyskinesia and a markedly decreased ejection fraction means a worsened prognosis during the acute phase of the disease. When the long term prognosis of a patient is considered a more thorough examination of the haemodynamic status seems to be warranted Even if the ejection fraction is found to be very low this does not necessarily mean that the patient needs to go into CHF A correlation seems to exist between prognosis ejection fraction and the relative cardiac volume. The greater the latter and the smaller ejection fraction the less are patients able to survive with as the cardiac output (CO) is a function of both these parameters and will be compensated for by the large volume.

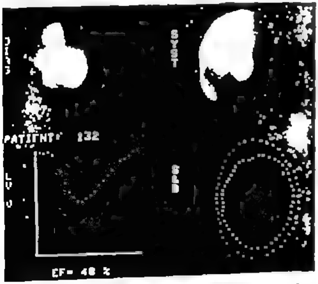

Figure 1 This figure demonstrates the end systolic and end diastolic frames after space and time correlation. The bottom right picture shows the automatic search and contour delineation

Other studies have been designed to detect early infarction in patient populations (Schad 1977). Radioisotope angiography has also been used in investigating angina pectoris populations (Borer *et al* 1977 Jengo *et al* 1980) at exercise and rest to determine what happens to an ischemic myocardium In this respect these studies have usually been combined with a ^{201}Tl perfusion study (Borer *et al* 1979 Bodenheimer *et al* 1980). From these studies it can be concluded the detection of abnormalities in left ventricular fraction at rest or during exercise is of great in detecting and diagnosing coronary heart disease some of these abnormalities occured in patients with normal ECG.s (Upton *et al* 1979) or even before the pathological ST segments appeared (Berger *et al* 197

Recently these nuclear methods have been used determining pharmacological interventions in patients with coronary heart disease and drugs tested have nitroglycerine (Salel *et al* 1976), beta blockers (Marshall *et al* 1977), Ca $^{++}$ antagonists, prenalterol (Boström *et al* 1980) and vasodilators amongst others The methods are ideally suited for these kinds of studies as they repeatedly are inherent in at least the gated quilibrium method

Another area where these radionuclide techniques have been very useful is in the diagnostics of CHF be it due to ischemic heart disease, valvular disease or cardiomyopathy and in the evaluation of therapeutic intervention with either vasodilators or digitalis.

PATIENT POPULATION

Thirty two patients 30 males and 2 females, 40 to 72 years old with a mean of 60 2 years were all examined with the gated equilibrium technique using a scintillation camera (Maxi-camera – General Electric USA), and ECG-gate and a computer system (PDP 11). All patients suffered from ischemic heart disease, but no one was examined during an acute phase of an infarction All the examinations were carried out ambulatory In all patients $^{99}Tc^{m}$ labelled red blood cells (Kabi Diagnostica, Sweden) was used All data were stored in the computer and the ejection fraction calculations were done according to a self employed computer programme technique with a horse

due to that they compensated themselves by having large cardiac volumes so that the CO and organ perfusion was maintained adequately (Figure 4). The value of a single ejection fraction determination ought to be a rather limited, but in combination with a volume determination of the cardiac chambers added information is given to the clinican, that might guide him in his therapeutic decision.

A wide usage of these non-invasive radionuclide methods will probably be seen in the future, with more sophisticated data processing programmes (Tobinick *et al* 1978, Verba *et al* 1980) and with even better gamma-cameras. Shortlived radioisotopes, derivatives of for example fatty acides (Poe *et al* 1976 Weiss *et al* 1977) may prove themselves to be superior in evaluating the events in the myocardium on a metabolic level and may come into use in the future as repeated evaluations with these radiopharmaceuticals are easier performed than with the radioisotopes of today

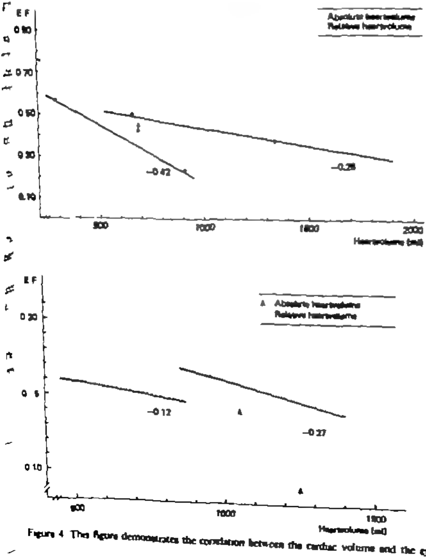

Figure 4. This figure demonstrates the correlation between the cardiac volume and the ejection fraction.

transmural infarction but who had no signs of cardiac failure but a huge aneurysm of the left ventricle (Figure 3). However he had a very large cardiac volume In the two patients with CHF low ejection fractions were found of 0.23 and 0.14 respectively They both improved on digitalis therapy

Of the five patients where pharmacological interventions were studied (Table II), two showed improved ejection fractions after therapy One of these patients received 0.5 mg nitroglycerin sublingually and the other a patient with severe angina pectoris was treated with a combination of propranolol and verapamil In the remaining three patients no detectable changes in the ejection fraction occured after pharmacological intervention

None of the patients in this group died even if the ejection fractions were low All patients with markedly decreased ejection fraction had dyskinetic areas based on their previous infarctions.

CONCLUDING REMARKS

Several studies have shown good correlation between ejection fraction measured by contrast ventriculography and gated equilibrium studies with $^{99}Tc^{m}$ labelled human serum albumine or red blood cells A correlation coefficient varying between 0.85–0.97 has been reported (Muroff & Freedman 1976 Folland *et al* 1977). It therefore seems adequate to assume that radionuclide angiography can be used safely and repeatedly to accurate evaluate left ventricular function By being a repetitive non-invasive method examinations can be carried out at minimal risk to the patients. In all published reports no adverse effects have been seen. The method can easily be adopted for routine clinical use and at the same time yield important pathogenetical and pathological information. In a routine use we found the method to be safe t... to handle, while important information was ob... Among the patient group several were considered f... coronary by pass surgery and the global left ve... cular function was then important to assess. N... the patients with markedly decreased ejection frac... were selected for by pass surgery as it was felt t... surgical intervention only gave good result in patie... with acceptable left ventricular haemodynamics ... close watch on the clinical status of the patients w... low ejection fraction was instituted so that therape... tic intervention when needed could be given imme... diately

One of the other applications which was used i... the patients was pharmacological intervention studie... Although only a small population was studied it w... quite feasible to use the radionuclide techniques f... evaluation of given therapy It can therefore be co... cluded that in patients with CHF radionuclide angio... graphy ought to be an important investigational to... as well as an instrument of judging given therap... One such area where experience has already be... gained is oncology Patients treated with adriamycin... may develop cardiac side effects amongst which a... CHF (Lefrak *et al* 1973) It has been found that the... patients early exhibit a decreased ejection fraction a... a marker of their cardiac insufficiency (Lessem *et a*... 1978). When the chemotherapy is discontinued th... ejection fraction returned to normal (Alexander *et a*... 1979), and the patients symptoms were eliminated

No correlation between the prognoses and the value... of the ejection fractions were found Even a low ejec... tion fraction did not necessarily mean that the patie... developed a CHF This was as has been said previous...

Table II The changes in the left ventricular ejection fraction after pharmacological intervention

Patient	Age	EF (prior)	Intervention	EF (after)
E.P	68	0.44	5.0 ml theofyllamine 80 mg propranolol	0.43
E.N	63	0.37	240 mg verapamil	
K.S	52	0.73	0.25 mg digoxin	0.71
O.S	56	0.17	0.5 mg nitroglycerine	0.17
S.H	56	0.57	0.5 mg nitroglycerine	0.65

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DISCUSSION

Availability of radionuclide technique

Rydén

Is this method easily available and not too difficult to use

Lessem

I believe that a computer is required to study CHF Unfortunately these are expensive and the computer programs get more and more difficult to work with. However the computers as such are not complicated to handle once you have acquired the skill and got used to them. The studies are repeatable. Results are also very reproducible. The computer programs are usually ready-made and the one I showed is available except for the part concerning early onset of mechanical systole.

Detection of impending CHF

Thaulow

We have tried the radioisotope technique examining some patients with positive exercise test and normal coronary arteries. We found that these patients could not increase their ejection fraction during exercise. These patients may have a preclinical cardiomyopathy that later may present itself as CHF Do you think your method can help to identify patients at risk before

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INVASIVE DIAGNOSTICS

Bo Liander

Congestive heart failure (CHF) is from a pathophysiological point of view a complex state with an insufficient cardiac output (CO) due to cardiac disease, an altered distribution of the CO, changes in the fluid compartments of the body and disturbances in the function of periferal organs (Davies 1965). The central factor is the cardiac insufficiency. I will here discuss the most frequently used methods for evaluating the cardiac factor in CHF with invasive techniques. Mostly I will deal with left ventricular insufficiency rather than cardiac insufficiency.

In most studies the performance of the heart is described in one of two ways. According to Starling's law, as modified by Sarnoff and others, the work performed by the ventricle per beat is determined by the preload and the contractility of the myocardium (Sarnoff & Mitchell 1962). In other situations one might be more interested in the control of the cardiac output (CO). The stroke volume (SV) (or CO) is then described as regulated by the preload, the contractility of the myocardium and the afterload (Cohn 1973). I will here discuss the variables used in clinical situations for the measurement of the terms used in these two concepts.

PRELOAD

The most correct expression for preload might be the length (or stretching) of the sarcomere at the end of diastole (Brady 1979), which is definitely not possible to measure in clinical studies. Two variables have been used as approximations of the end diastolic sarcomere length. These are:

The end diastolic volume (of the left ventricle — LVEDV)

LVEDV can be measured with reasonable accuracy during angiocardiographic studies (Sandler 1970). It cannot, however, be measured during a routine catheterization. In angiocardiographic studies an increased LVEDV has been used as a sign of decreased left ventricular function. There is, however, no constant relation between the sarcomere length and the LVEDV. For example: In chronic aortic or mitral insufficiency the enlargement of the left ventricle is probably due to the development of new sarcomeres in series with the old ones. An enlarged LVEDV does thus not necessarily reflect an increased sarcomere length in these cases. In patients with coronary heart disease, an expanded scar after a myocardial infarction (MI) may enlarge the ventricle, and an increased LVEDV (or decreased ejection fraction) does not in such patients necessarily correlate to the degree of myocardial failure.

The filling pressure of the left ventricle

The level of the filling pressure depends both on the length of the sarcomere and the distensibility of the myocardium. Thus, an elevated filling pressure does not necessarily reflect the degree of sarcomere stretching (Braunwald & Ross 1963). The filling pressure can, however, be measured more easily than the LVEDV and is therefore extensively used as a measurement of the preload.

The filling pressure is best measured as the left ventricular end diastolic pressure with a catheter in the left ventricle. The technical details should be considered carefully. Especially in patients having ventricles with a low distensibility, the difficulties in obtaining reliable records may be considerable, especially at increased heart rate.

The left ventricular filling pressure can also be estimated by using a catheter in the pulmonary artery or in the pulmonary artery wedge position. This technique is often used, thus substantially simplifying the catheterization procedure. The recorded pressure is in

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they get clinical symptoms This could be of great help if we are trying to start vasodilator treatment at an earlier stage than we do today

Lessem

There have been studies by Leppo and coworkers (1980) and by Hamilton (1980) and Lyons & Olson (1980), showing that patients who on angiography showed normal coronary arteries, but who at exercise developed akinetic or dyskinetic areas not necessarily increased their ejection fraction These studies have also shown that some of the patients tended to go into CHF later on. I therefore believe that if you do not increase your ejection fraction during exercise and develop an akinetic or dyskinetic area during the stress test this is a good indicator for when treatment against CHF should be instituted

Various isotopes

Swedberg

One interesting aspect of the radio-nuclide methods is that you can use different isotopes to analyse [illegible] ferent questions. I wonder if you think there are [illegible] new isotopes in the future which will give more [illegible] lights to CHF Secondly another possibility is [illegible] other kinds of radiation i.e. you can look at the [illegible] radiation. What are your comments upon that [illegible]

Lessem

New radio-nuclides are developed all the time [illegible] of the most exciting aspects of this whole conce[illegible] the possibility to study the cardiac metabolism [illegible] positrons. This technique is so far not available [illegible] clinical use. It has been developed especially by [illegible] Sobel group in St Louis (Lerch *et al* 1980) I beli[illegible] that in the future of nuclear cardiology this is proba[illegible] the direction we will see a lot more of Thallium [illegible] the combined thallium and cardiac hemodynamic s[illegible] dies done at exercise has been shown to be one [illegible] the most safe and accurate methods to determine [illegible] status of the cardiac muscle.

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rely limited in empirical value (Brady 1979)

The rate of rise of the left ventricular pressure depends both on the velocity of shortening of the contractile element and on the properties of the elastic components in the myocardium. The properties of these components may vary considerably between individuals (Braunwald & Ross 1963)

The rate of pressure rise is influenced by changes in the preload and in the afterload (Wallace et al. 1963).

The route of depolarisation of the left ventricle effects the rate of pressure rise (Sarnoff & Mitchell 1962)

The normal range of the indices derived from isovolumic pressure curves is wide (Braunwald & Ross 1979)

Only pressure curves obtained by the use of high frequency recording catheter tip manometers should be used for these calculations (Braunwald & Ross 1979). Even if an ordinary pressure recording system can be shown to have qualities good enough during ideal conditions, the system is so susceptible to external disturbances (as catheter whip artefacts or minor air bubbles in the system) that one cannot be sure of the properties of the system at the moment of the pressure recording.

The clinical value of contractility indices derived from pressure recording thus seems to be limited.

THE AFTERLOAD

The afterload is defined as the tension (or strictly speaking, the stress or force/cm^2) in the ventricular wall during contraction (Mirsky 1979). This tension (stress) is a complicated function of the instantaneous intracavitary pressure and the instantaneous size (form, and wall thickness of the ventricle. However in clinical practice the afterload is mostly simplified as the product of pressure times volume (Mirsky 1979).

As the left ventricular volume cannot be measured during a routine catheterization, the afterload is often approximated to the systolic blood pressure. In so doing, one should be aware of the not insignificant simplification.

THE CARDIAC OUTPUT

As an insufficient CO is the central factor in CHF and as the SV is often used in Starlings relations a reliable method for CO determination is essential when studying patients in CHF. The SV cannot be measured directly but should be calculated as a mean value over the period of time when the CO is determined. The methods most often used for determining CO are:

The direct Fick principle

This method has been widely used, and is reproducible, but the method takes considerable time. It requires one catheter in the pulmonary artery and one in a peripheral artery and the collection of oxygen in the expired air (Hamilton 1962)

Indicator techniques

The indicators used are either dye or cold (Hamilton 1962). During the last few years thermodilution has been widely used, probably because of its repeatability because with the technique commonly used only one catheter is needed and because of the development of automatic devices for the calculation of the CO (Forrester et al. 1972). The calculation of the CO involves an extrapolation of a declining part of the temperature curve to a base value or line. For the precision of the method the performance of this procedure is important. The extrapolation becomes more difficult and the possibility of error is larger when the CO is small and in cases of valve insufficiencies (Hamilton 1962). When using an automatic device it seems essential to control visually how the extrapolation is done in order to be able to discard obviously wrong curves.

It has been shown, however, that properly used thermodilution can give as reliable results as the direct Fick and dye dilution methods (Forrester et al. 1972)

METHODS FOR REPORTING RESULTS

Two methods are used. In the first, the individual patients are plotted in a Starling diagram, in which some variable for the energy released (often SV or SW) is plotted against some variable for the preload (often left ventricular filling pressure), and the change caused by an intervention is noted. In the second, the mean values and the range (or the individual values) of the variables studied before and after the intervention are given in tables. The second method seems to be the most popular at the moment. Whichever method used, there are difficulties both in pre

these cases also influenced by the pulmonary vascular resistance. As this resistance might vary for example during the use of vasodilating agents presently studied in left ventricular failure (Rubin & Peter 1980) a change in the pulmonary artery or pulmonary artery wedge pressure does not necessarily reflect an altered preload of the left ventricle.

The pressure recording is often of not so good a quality as that obtained with a catheter in the left ventricle.

Pressures recorded on the right side of the pulmonary capillaries should thus be used with some care when studying the left ventricular filling pressure.

THE WORK PERFORMED BY THE VENTRICLE

Starling used the expression "the mechanical energy set free" at contraction but in his experiments he actually studied changes in stroke volume. When studying the organism as a whole the oxygen uptake is used as the best measure of the energy set free. The oxygen uptake of the heart is, however quite difficult to determine. Thus, in clinical studies other more easily measurable variables related to the energy released are used. Among those are:

Stroke volume (SV)

Changes in the SV are known to influence only to a small degree the oxygen uptake of the myocardium (Evans & Matsuoka 1915). In studies on afterload reduction the relation between SV and filling pressure often changes with changing afterload (Cohn 1973). Such a change should not be interpreted as reflecting an altered myocardial function, but only a new relation between the factors determining the energy released by the myocardium (as SV and generated tension).

As an expression of the load on the heart the SV is thus of limited value.

The pressure generated by the myocardium

It is well known from clinical studies that the oxygen uptake of the myocardium is well correlated to the systolic blood pressure (Holmberg 1979).

Stroke work (SW) or stroke volume multiplied by systolic blood pressure

This variable, being a product of two factors of unequa importance for the oxygen uptake of the heart is les valuable as an expression of the mechanical energ set free by the ventricle. One and the same SW ca on different occasions in the same heart obvious represent very different amounts of oxygen uptake o the heart. In my opinion SW is of limited value an should not be used in Starling relations.

The most useful simple variable for estimating th energy set free by the ventricle might be the pressur generated by the myocardium.

CONTRACTILITY

The contractility can be defined as the capacity of the myocardium to do work. In many clinical settings a knowledge of the contractility of the myocardium can be of value. A change in contractility can be implied when there is a change in the stroke volume without any change in preload or afterload (Braunwald & Ross 1979), or when in a Starling diagram the curve relating the energy set free to the preload is changed (Braunwald & Ross 1979).

The degree of contractility is also reflected by the velocity of shortening of the contractile element in the myocardial cell (Braunwald & Ross 1979). For several years one has tried to find indices which are measurable during a catheterization and which would directly reflect changes in the velocity of contraction of the myocardium (and thus changes in the contractility). The rate of pressure rise during the isovolumic phase of the ventricular contraction must in some way be related to the velocity of shortening of the contractile element in the myocardial cell (Gleason & Braunwald 1962). A number of different indices derived from this part of the ventricular pressure curve has been used to estimate the velocity of shortening of the contractile elements (Braunwald & Ross 1979). Several objections can however be raised to the use of such indices:

1) Brady in the latest edition of Handbook of Physiology says, that the force velocity relation in heart muscle may be a concept without fundamental significance in defining myocardial function and also se-

erely limited in empirical value (Brady 1979)

) The rate of rise of the left ventricular pressure depends both on the velocity of shortening of the contractile element and on the properties of the elastic components in the myocardium. The properties of these components may vary considerably between individuals (Braunwald & Ross 1963)

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This method has been widely used, and is reproducible but the method takes considerable time, requires one catheter in the pulmonary artery and one in a peripheral artery and the collection of oxygen in the expired air (Hamilton 1962).

Indicator techniques

The indicators used are either dye or cold (Hamilton 1962). During the last few years thermodilution has been widely used, probably because of its repeatability because with the technique commonly used only one catheter is needed and because of the development of automatic devices for the calculation of the CO (Forrester *et al* 1972). The calculation of the CO involves an extrapolation of a declining part of the temperature curve to a base value, or line. For the precision of the method the performance of this procedure is important The extrapolation becomes more difficult and the possibility of error is larger when the CO is small and in cases of valve insufficiencies (Hamilton 1962) When using an automatic device it seems essential to control visually how the extrapolation is done in order to be able to discard obviously wrong curves.

It has been shown, however that properly used thermodilution can give as reliable results as the direct Fick and dye dilution methods (Forrester *et al* 1972).

METHODS FOR REPORTING RESULTS

Two methods are used. In the first, the individual patients are plotted in a Starling diagram, in which some variable for the energy released (often SV or SW) is plotted against some variable for the preload (often left ventricular filling pressure), and the change caused by an intervention is noted. In the second, the mean values and the range (or the individual values) of the variables studied before and after the intervention are given in tables The second method seems to be the most popular at the moment. Whichever method used, there are difficulties both in pre-

senting and in interpreting the results and one should be aware that the results are often influenced by changes in more than one studied variable.

CONCLUSIONS

Invasive techniques can be used to study patients in CHF. As with all techniques there are drawbacks. When used properly and with care, however the curacy of invasive methods can be good.

The use of invasive techniques might be of spe value in studying patients in incipient CHF and evaluating the results of acute therapeutic interv tions in patient in CHF.

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DISCUSSION

Determination of CO

Rydén

You are quite positive about thermodilution as a method for CO determination? This method may work at rest but what should be used during exercise? I think in the future we have to study the patients more at work and we really have to develop a method for CO during these conditions. Is thermodilution accurate?

Lilander

I do not know. My own experience with thermodilution is limited. When I studied patients at work I used dye dilution or the direct Fick method. I believe that thermodilution can give results which sometimes seem to be inaccurate.

Holmgren

We have spent a lot of energy on this problem. I our studies of angina pectoris we always measure CO

th at rest and during a submaximal work load. With our thermodilution machine CO agree well with those obtained with direct Fick up to 10 l/min. When you reach 15 l/min marked deviations can occur. I think should use either direct Fick or dye dilution in exercise studies unless one can show a good agreement between thermodilution and either of these methods.

Fischer Hansen

I am surprised that you have no problems with thermodilution at rest. Patients in severe CHF often have a very large volume of the right side of the heart and a low CO. Everyone knows that in this situation it is difficult and often impossible to measure CO with dilution techniques. You can use the direct Fick method but even this is not free of problems since there is a variation from minute to minute in CO. I think that you should warn against the use of the dilution technique in the resting situation in patients with severe CHF.

Lünder

I agree. From a theoretical point of view the dilution methods are difficult to use with small CO.

Pulmonary artery oxygen saturation

Holmgren

In the morning session, Werkö stressed the importance of taking peripheral circulatory changes into account. When discussing invasive procedures I think most people seem to avoid the simplest measure that can be used — the oxygen saturation of mixed venous blood or arterio-venous oxygen difference. I think this parameter gives a lot of very solid information on which one could base judgement of the condition of the heart.

Fischer-Hansen

We are looking for simple parameters to control the results of specific treatment. We do not need very sofisticated invasive methods. I think we need two figures from which it is possible to tell very much about the results of the treatment. These are the left ventricular end diastolic filling pressure and the pulmonary artery oxygen saturation. These parameters are closely correlated to the functional status of the patient. Other parameters mentioned show poor correlation to the status of the patient and are difficult to obtain. Of course, the more sofisticated parameters may be of value in scientific conditions when we are trying to evaluate drug effects.

Lünder

With regard to the idea of using the oxygen saturation in the pulmonary artery as a measure of CO, are there any investigations showing the correlation between changes in CO and changes in oxygen saturation in the pulmonary artery in these very sick patients.

Werkö

Already in 1949 it was demonstrated that you could treat acute pulmonary edema with digoxine (Harvey *et al.* 1949, Lagerlöf & Werkö 1949, Werkö *et al.* 1953). In profound left ventricular failure you will find a rapid increase in the oxygen content of the mixed venous blood and a rapid decrease in pulmonary arterial pressure. There is no question that there is a good correlation between the relief of acute failure and these two parameters. There has been sophisticated studies done with more and more complicated computerized methods but still some of the fundamental measures are the pressure behind the ventricle and the peripheral distribution of blood flow which is showing up in the oxygen concentration in the pulmonary artery.

Peripheral circulation

Cohn

It might be appropriate to make a comment consistent with the title of the symposium. The fact that this conference aimed at vasodilators shows that the peripheral circulation has a very important effect on cardiac performance. Still, all the discussion has been related to the study of the heart and there has been no discussion of the peripheral circulation. Although difficult to do I think that we are entering an era when we need to develop more precise techniques for looking at the small vessel vascular resistance. I think it is important to recognize that the drugs we are going to talk about have direct effects on the periphery and secondary effects on the heart. If we could define the peripheral effects of the drugs more precisely we might not even have to study the heart.

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Hydralazine and myocardial contractility

Andersson

I have a specific question to Dr Chatterjee: Does hydralazine clinically have a positive inotropic effect? I think your answer is "no" because you found on the papillary muscle that very high concentrations were needed. Such concentrations are not expected during therapy. The point is: If you look at isolated vessels you do not find a dilating effect until you reach concentrations with which you have a positive inotropic effect in the papillary muscle. There must be something in this which we cannot explain. Maybe hydralazine is not active per se but through one or more of the metabolites. I do not think you could base your conclusion that it has no positive inotropic effect on that particular experiment.

Chatterjee

I did not make that conclusion. I said that in isolated papillary muscles there is no positive inotropic effect. This is similar to studies with phentolamine. On isolated papillary muscles there is no positive inotropic effect. This is similar to studies with phentolamine. On isolated papillary muscles there was no change in force development and actually with high concentrations it declined. When phentolamine is administered directly into the coronary arteries a positive inotropic effect can be demonstrated. I do not know the mechanism.

Rebound phenomenon after cessation of hydralazine

Fischer-Hansen

When you stopped treatment with hydralazine did you see the rebound phenomenon which has been described after end of treatment with prazosin

Chatterjee

In most patients the private physicians stopped hydralazine so I cannot comment on rebound phenomenon. We looked at another group of eleven patients who were admitted to the hospital. In these we discontinued hydralazine under supervision. We did not see any dramatic worsening of the hemodynamics. For instance it took an average of 40 hours before we saw a significant decrease in CO

Heart size and response to vasodilators

Fischer-Hansen

It has been stated that heart size on chest X-ray might be a good predictor of the effect of vasodilating treatment. Is it necessary to perform complicated hemodynamic investigations or could you just use a chest X-ray

Cohn

I think a large ventricle favours the likelihood of a good response to hydralazine or any vasodilator. The more dilated the left ventricle is the better the response to drug. In such cases we are dealing with bad systolic and good diastolic function. If the heart is small but the patient symptomatic it is probably a patient with changes in the filling characteristics of the ventricle which probably is not much altered by vasodilation.

Vasodilators and edema

Fischer-Hansen

It has been claimed that in vasodilator therapy it is often necessary to add further diuretics. Dr Chatterjee, what is your experience in your group of 60 patients. Did you often have to increase the diuretic therapy because of edemas induced by venodilation

Chatterjee

Many patients had their diuretics increased by their private physicians who also stopped the vasodilators. Of the eleven patients who were followed and restudied by us about half had their diuretics decreased. In three patients the dose was increased due to edema. Surprisingly we found improved hemodynamics also in these patients with a higher CO in the late catheterization than in the acute. This phenomenon has been described in literature for many vasodilators and is not unique for nitrates and hydralazine. This late fluid

accumulation and weight increase probably takes place despite an increase in CO

Vasodilators and coronary perfusion

Hutton

We have been working with a new vasodilator similar to hydralazine. It was tested in patients with coronary heart disease but not in CHF. We found similar effects in the coronary as in the systemic circulation, with large increases of coronary flow and a big reduction of coronary vascular resistance. Dr Chatterjee in your class III and IV CHF patients, why do you think you found no difference in coronary flow or myocardial oxygen consumption as compared with my patients not in CHF?

Chatterjee

I do not think I can give a precise answer to the question but I may speculate. I think it is a significant difference between the effect on the coronary vascular bed alone and the changes which determines the myocardial oxygen demand. This may really be very important when you evaluate the effect of vasodilation in patients with coronary heart disease. I do not have any experience of hydralazine in patients without CHF. Nitroprusside when given to a person without coronary heart disease and without CHF significantly increases coronary blood flow with an important reduction in coronary vascular resistance. If nitroprusside is administered to patients with severe CHF in many cases there is a reduction in coronary blood flow as the CO increases.

It seems to me that in patients with CHF the reduction of the arterial pressure probably is an important determinant of changes in the total coronary blood flow. The problem is that although we may demonstrate unchanged coronary blood flow and myocardial oxygen consumption this is no answer to the question what really happens with the ischemic myocardium. The only thing we can go by is that there is no clinical deterioration in any of the patients treated. None developed angina and therefore we can assume that there was no deterioration in myocardial oxygen transport induced by the vasodilators.

Ejection fraction as a measure of efficacy of vasodilation

Wikstrand

In your study of patients with mitral insuffic[...] there was a decrease in the regurgitation and in[...] crease in output. In these patients you noticed an [...] changed ejection fraction in spite of a consider[...] improvement in left ventricular function. This ejec[...] fraction can be very misleading in patients w[...] changes in mitral regurgitation is not carefully [...]corded

Chatterjee

There was no acute change in ejection fraction[...] total stroke volume and the left ventricular end [...]stolic volume did not change. Therefore the calcul[...] ejection fraction remained unchanged. There w[...] redistribution of the total stroke volume. Chroni[...] on the other hand the forward stroke volume rema[...] elevated while the end diastolic volume decrea[...] This means that there was a redistribution of the [...] stroke volume of the left ventricle. More blood [...] being pumped forwards into the aorta and less b[...]wards into left atrium.

I also want to emphasize another point. An incr[...] of ejection fraction does not automatically mea[...] increased CO. It may depend on a decrease in [...] diastolic volume. You may in fact have a red[...] ejection fraction but maintained stroke volume [...] not think we should utilize changes in ejection frac[...] to express a change in CO

Awan

With regards to your comments on ejection frac[...] I agree. I think that unless one has a knowledg[...] the enddiastolic volume the interpretation of cha[...] on ejection fraction can be difficult

Is there a sustained effect of prazosin or not?

(See also page 152)

Rydén.

In a study of the acute and chronic effects of praz[...] we made hemodynamic investigations at the ins[...]

of treatment and three months later. Our results not correspond to those presented by Dr Awan. ere was an excellent response in the acute phase this was much attenuated at the follow-up. It is y difficult for me to understand why patients are proving in a chronic study when many investigators us have shown that the response is much less ary when restudying the patients later on. Do you nk that this tachyphylaxis is a matter of dosage. you start with a very small dose, do you think the nger of developing tachyphylaxis is the same.

Awan

fore I can answer your question, I would like to ow more about your initial hemodynamics, the initial responses and what was observed subsequently. ne of the problems that I see is that if you take patient with mild to moderate CHF you might call em symptomatic class IV. If the hemodynamic abnormality is moderate or mild at start the vasodilator s only mild effects. The effects are more pronounced uring exercise but the resting effects are very mild.

Swedberg

hey all had high filling pressures, many of them ove 20 mm Hg. CO was low. Their hemodynamics nproved substantially during the acute study and ey also seemed to improve clinically during the first art of the observation period. When restudying them ree months later with recatheterisation we did not et an impression of improved clinical condition or ubstantially improved hemodynamics. They did not art better off than they did from the beginning. Thus, e were disappointed with the prazosin effect.

Awan

I do not know how to explain it. Most studies I am are of have shown beneficial effects which were maintained.

Hansteyer

Did you keep your diuretic dose constant during the estudy. My reason to ask is that in couple of studies demonstrating sustained beneficial response of prazosin in terms of exercise tolerance nine of ten patients had to increase the amount of diuretics to maintain the response.

What I wonder is: Do you think that prazosin has a slightly more venodilating effect and that adding diuretics potentiates this effect? It might be difficult to know to which extent the effect is a venodilating effect of the diuretics.

Awan

I am not aware of any long-term double-blind or single-blind study that has been designed to answer that question.

Diuretical requirements in our experience mostly increased whether it was nitrates or hydralazine or prazosin. I think this is something which occurs very commonly with most of the asodilators. Diuretic requirements seems to be reduced with catecholamines which is the only vasodilator I know of associated with reduction in diuretic requirement.

Cohn

One of the problems is that the complexity of CHF makes it difficult to assess in general the response to treatment in the small sample of patients in a particular study. It is clear to me that prazosin is a drug that is very effective in some patients and much less effective, perhaps ineffective in others. We may all observe patients who have a dramatic initial response and in whom in some respects the clinical response diminishes. In a series of eight or ten patients you may just by chance get more good responders than bad ones. If so you will notice a sustained effect of prazosin. I do not think that we so far have data from such a large series of patients that we can make subsets of patients according to etiology, hemodynamic background, age, the degree of coronary heart disease and so on. If there is an important occlusion of a proximal coronary artery the situation may perhaps be aggravated by a small fall in perfusion pressure as an example. I think all vasodilators have to be looked at in large series of patients before we know which drug is effective in a particular situation.

The disagreements that we find from separate studies probably to a large extent reflect minor differences in the study design and perhaps major differences in patient characteristics.

Secondly and perhaps of greater importance is the fact that we are fast getting beyond the hemodynamic stage of study of these drugs It is clear that every vasodilator may produce the desired hemodynamic response but the important thing really is clinical efficacy I think the efficacy should be assessed by something else than changes in CO and ejection fraction Carefully designed controlled double blind studies over a reasonable period of time are necessary before we can decide where these drugs will fit in our general clinical practice.

Should the mechanism behind the increased vascular resistance influence the choice of vasodilator?

Andersson

Is it not astonishing that specific blocking agents like noradrenaline blocking agents, alfa-adrenoceptor blocking agents and for example captopril have any effect at all in CHF There is a multifactonal genesis to the increased systemic vascular resistance in these patients. If you block one of these factors the other one could very well take over and after some time the vascular resistance could increase again to the previous magnitude. Has anyone looked at prazosin patients who did not respond after an initial period? Do they have an increased renin or angiotensin concentration in blood as a compensatory mechanism? Can this be an explanation to tolerance development?

Cohn

These remarks are important We are beginning to do such investigations but so far we do not have data enough to know whether resistance to any of the drugs is caused by the activation of other systems This problem of multiple systems controlling the vascular resistance has been known in the treatment of hypertension for years It has led to the combined drug treatment of high blood pressure. Hopefully it will be less complicated in CHF In these patients we seem to have a better understanding of the systems activated and probably they may not be as complex as in hypertension Captopril does indeed have a sustained effect When captopril is administrated chronically it appears to be effective in patients with low plasma renin both in hypertension and in CHF which rises the possibility that some other system is infl… by captopril as well as the renin-angiotensin s… Prazosin is identified as an alfa-receptor bl… would be surprised if in the long run, we d… discover that prazosin influences other vaso-co… tor mechanisms as well We may begin to distu… two or three factors influenced by each of these… The acute response may depend on one … lc response on another factor When you give th… dose of prazosin to hypertensive patients ther… up and faint. This dramatic alfa-receptor block… tion is what you can expect with this drug. Af… or three days of prazosin therapy the patient… up but does not faint. Something has correct… orthostatic response. Patients with CHF stand… usually do not drop their blood pressure at all… started on prazosin. The patient with CHF do… raise his plasma noradrenaline and plasma re… tivity in the standing position which normals… we block the renin and the noradrenaline rise in… subjects they faint. In CHF the up-right positio… not stimulate the sympathetic or renin-angiotens… tem and consequently prazosin does not result… thostatic hypotension. We have so far been … norant about the control of the vascular resistance… we are using these drugs.

Andersson

When using vasodilators in CHF and consideri… multifactorial genesis to the increased system… cular resistance would it not be more attractive… drugs like hydralazine rather than more specific… like captopril or prazosin, or can we not draw… a conclusion?

Cohn

I guess you cannot. I am not sure that hydr… necessarily is more attractive because it is non sp… On the contrary you can easily claim that th… thing is to interfere with the particular system… is stimulated if this is possible over a chronic… period

Andersson.

Then you should rather use inotropic drugs whic… to some extent decrease the release of humoral … increasing vascular resistance

[..]berg.

[..]ardial failures develop because we are not con[..]led for the increasing systemic vascular resist[..] I wonder if in the future it will be possible to [..] the myocardium per se and to protect it from [..]re.

[..]

[..]ll be possible. I think the most exciting future [..]lopment of vasodilator therapy is not in treating [..]lass III and IV CHF patients that we have been [..]ng about today. These patients have a very limited [..]xpectancy whatever we do. I think the excitement [..] prevent the development of CHF in a patient [..] myocardial damage. I think that we will be suc[..]ful if we alter the feed-back mechanisms which [..] to CHF in the presence of myocardial disease. [..]assical example is the patient with myocardial in[..]tion who has little signs of dysfunction during the [..]e stage, goes home and is fine. Three months later [..]resents with shortness of breath and peripheral edema. As far as we know nothing has happened during that 3-month period to the myocardium. What I think has happened is that the positive feed-back system has stressed the myocardium into CHF. I think that the drug therapy has a potential for altering this history. How to study it I am not sure. It is an extremely difficult thing to study people before they develop overt CHF and to demonstrate that it can be prevented. Anyhow I think the potential is there and that is indeed where I think the impact of this whole approach can be achieved.

Andersson

Then you would suggest a comparison between digoxine and one of the vasodilators in patients with mild to moderate CHF?

Cohn

We have been using digoxine for years. Still we have all these people with severe progressive CHF which is the most common cause of death in our society. I would hope a new form of therapy could be more effective.

Secondly and perhaps of greater importance is the fact that we are fast getting beyond the hemodynamic stage of study of these drugs. It is clear that every vasodilator may produce the desired hemodynamic response but the important thing really is clinical efficacy. I think the efficacy should be assessed by something else than changes in CO and ejection fraction. Carefully designed controlled double-blind studies over a reasonable period of time are necessary before we can decide where these drugs will fit in our general clinical practice.

Should the mechanism behind the increased vascular resistance influence the choice of vasodilator?

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Is it not astonishing that specific blocking agents like noradrenaline blocking agents, alfa-adrenoceptor blocking agents and for example captopril have any effect at all in CHF. There is a multifactorial genesis to the increased systemic vascular resistance in these patients. If you block one of these factors the other one could very well take over and after some time the vascular resistance could increase again to the previous magnitude. Has anyone looked at prazosin patients who did not respond after an initial period? Do they have an increased renin or angiotensin concentration in blood as a compensatory mechanism? Can this be an explanation to tolerance development?

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Andersson

When using vasodilators in CHF and considering the multifactorial genesis to the increased systemic vascular resistance would it not be more attractive to use drugs like hydralazine rather than more specific drugs like captopril or prazosin, or can we not draw such a conclusion?

Cohn

I guess you cannot. I am not sure that hydralazine necessarily is more attractive because it is non-specific. On the contrary you can easily claim that the best thing is to interfere with the particular system which is stimulated if this is possible over a chronic time period.

Andersson

Then you should rather use inotropic drugs which will to some extent decrease the release of humoral agents increasing vascular resistance.

rg'

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Anderson.

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We have been using digoxine for years. Still we have all these people with severe progressive CHF which is the most common cause of death in our society. I would hope a new form of therapy could be more effective.

PHARMACOLOGICAL ASPECTS ON THE TREATMENT OF CHF

Karl-Erik Andersson

ymon clinical manifestations of congestive ure (CHF), peripheral hypoperfusion and pul- congestion, each has its specific and variable namic cause. Traditional pharmacological it (Table I) has since long been directed against mptoms, aiming at improvement of cardiac CO) by drugs increasing the contractility of cardium, and reduction of left ventricular end- : and pulmonary venous pressures by means tics. The main therapeutic principle has been myocardial "stimulation" by means of cardiac es, whereas diuretic "unloading" of the heart less has been a complement to this therapy.

' the traditional therapy has been successful cases of both acute and chronic CHF, patients ry to treatment with cardiac glycosides and di- are not uncommon, and even in responders apy side effects are frequently encountered. the last decade, the principles and agents used tional treatment of CHF have been critically , leading to a better understanding of the me- ms behind cardiac failure, and to the introduc new pharmacological means to treat this dis-

aims of the present review are to focus on some ms and questions associated with traditional ent and to give some pharmacological aspects rapeutic alternatives, including vasodilators.

I Traditional therapy of CHF
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I. TRADITIONAL THERAPY

1 *Cardiac glycosides*

According to the traditional text-book view cardiac glycosides are indicated in all forms of CHF irrespec tive of the cause and whatever the rhythm (Chung 1971 Moe & Farah 1975), "digitalis being "the key to effective therapy for heart failure (Walker 1974). For several reasons, this view has been challenged by many authors (e g Cohn 1974 Guz & MacHaffie 1978, Hamer 1979 Johnston & McDevitt 1979)

● *Mechanism of action* Despite extensive research, the exact mode of action of cardiac glycosides in producing their positive inotropic, negative chronotropic and tox ic actions on the heart has not been elucidated (see, e g. Lee & Klaus 1971 Langer 1977 Akera & Brody 1978) One of the questions that remains to be settled is whether the positive inotropic and toxic actions are mediated through the same mechanism (see e g Günthert & Linde 1977). Most workers seem to favour the view that Na^{+}–K^{+}–ATPase in the myocardial sar colemma is the digitalis receptor (Akera & Brody 1978). A current hypothesis is that cardiac glycosides by binding to and inhibition of this enzyme reduce the sodium pump activity leading to a transient in- crease in the intracellular concentrations of sodium (Figure 1) The increase, which occurs only during the early phase of the cardiac cycle, results in an en- hanced calcium influx This, in turn, leads to a rise in the concentration of free calcium available to the contractile proteins and an increase in contractility (Akera & Brody 1978). Supporting this hypothesis, electrophysiological evidence has been presented sug gesting that digitalis inotropy is associated with en- hanced slow inward calcium current (Weingart *et al.*

*From the Department of Clinical Pharmacology, University Hospital Lund, Sweden

1978) This, however does not seem to be the only mechanism of importance as the inotropic effect of cardiac glycosides is not lost in the presence of e.g. verapamil which is an effective blocker of slow inward calcium current (Kohlhardt *et al* 1975). An enhancement of slow inward current by adrenoceptor stimulants (Reuter *et al* 1967 Vassort *et al* 1969) is thought to play a major part in the positive inotropic effect produced by these drugs (Tälen 1977).

● *Characteristics of the inotropic action* A positive inotropic effect of cardiac glycosides is well documented *in vitro* as well as *in vivo* in animals and in man, and in normal and abnormal hearts (Smith & Haber 1973) It should however be emphasized that the increase in contractility that can be obtained by digitalis in therapeutic dosage is only a fraction of that produced by beta adrenoceptor agonists (Beiser *et al* 1970 Kleiman *et al* 1978) or by mild exercise (Davidson & Gibson 1973). The relatively small positive inotropic action of cardiac glycosides is a factor to take into consideration when discussing the clinical indications for these drugs.

The positive inotropic effect of e.g. intravenous digoxin is not immediate, but can be demonstrated within 10 to 15 minutes; its peak effect is generally obtained within 30–90 minutes Few therapeutic advantages is considered to be gained by using a rapidly acting glycoside preparation (Forrester & W... ters 1978), and digitalis is often considered a ... measure in the treatment of acute cardiac failure (... mirez & Abelman 1974).

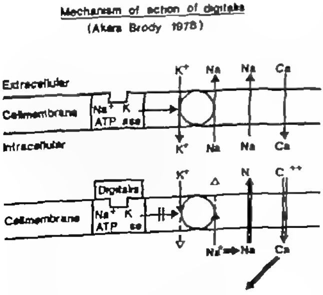

Figure 1 Mechanism of action of digitalis.

It is generally accepted that digitalis acutely ... creases myocardial contractility both in the failing and non-failing heart. However in patients with chro... CHF (cardiomyopathy or ischemic heart ... dergoing cardiac catheterization for 4 h Cohn (1975) showed that acute digitalization 0.5+0 5 mg) did not necessarily lead to cons... marked or lasting hemodynamic improvement Dav... idson & Gibson (1973) using a phonocardiographi... thod of evaluation found a transient positive ... effect in patients with aortic Starr Edward... treated with oral digoxin for 10 days. After the f... administration, no significant positive inotropic e... attributable to digoxin could be demonstrated desp... plasma digoxin levels within the therapeutic ran...

Several studies have shown that mainten... oxin therapy for patients with CHF and sinus ... can be discontinued without clinical deteriora... many patients (Dall 1970 Hull & McIntosh ... Johnston & McDevitt 1979). Furthermore, Ford *et* ... (1979[a, b, c]) presented evidence that the changes o... curring in red blood cells of patients during the ear... stage of digoxin therapy did not persist in the ... term If this effect on erythrocyte Na^+–K^+–AT... ase corresponds to that exerted by digoxin in the myo... cardial cell is not known. However all these ... raise the question whether or not the cardiac effects of digoxin persist during long term treatment

Crawford *et al* (1976) showed by echocardiography that in normal man, treated with digoxin for 10–1... days, the drug caused a maintained positive inotropic effect. Kleiman *et al* (1978), using fluoroscopic an... alysis of the motion of surgically implanted myocardial markers in the wall of the left ventricle, found that in patients with stable coronary artery disease chron... oral digoxin treatment exerted a sustained positive in... otropic effect that persisted for at least 4 weeks and was equivalent to that achieved with rapid intravenous digitalization. In patients with heart disease, being ... scribed digoxin for CHF and who showed clinical ev... dence of deterioration on placebo Dobbs *et al* (1 ...

found that digoxin caused a shortening of left ventricular ejection time which persisted for at least a month.

Obviously some patients treated for CHF benefit from the therapy (Dobbs *et al.* 1977 Meister *et al.* 1980) and some do not. This does not mean that an established therapy should be discarded, but rather that the indications for chronic digoxin therapy should be critically re-evaluated.

It is important to emphasize that an increase in myocardial contractility is not always reflected by an increased CO as contractility is only one of the determinants of cardiac performance, the others being preload, afterload and heart rate (Cohn 1974 Mason 1978) Even if cardiac glycosides cause acute increases in myocardial contractility also in the non-failing heart, they do not always increase CO. In cardiogenic shock cardiac glycosides did not significantly increase CO and were less effective than isoprenaline (Cohn *et al* 1969) Also in left ventricular failure in myocardial infarction (Balcon *et al* 1968 Hodges *et al.* 1972, Rahimtoola *et al.* 1972, Lipp *et al* 1973), and in cor pulmonale (Schüren & Hüttemann 1974 Green & Smith 1977) little benefit seems to be gained by cardiac glycosides These drugs may rather be harmful as the increase in contractility is not always counterbalanced by a reduction in heart size (see Marcus 1980).

Vascular effects All the commonly used cardiac glycosides can induce contraction of isolated vascular smooth muscle from animals (Leonard 1957 Brokaert & Godfraind 1973 Quest *et al.* 1976 Nakajima *et al* 1977 Flaim *et al* 1979) as well as man (Mikkelsen *et al* 1979a,b) both by a direct action on the smooth muscle cell and by causing release of noradrenaline. Also the drugs have been able to produce arteriolar constriction in every vascular bed that has been tested (Ross *et al.* 1960a,b Braunwald *et al* 1961 Ferrer *et al* 1965 Harrison *et al* 1969 Vatner *et al* 1971 Lewinsky *et al* 1975 Brecht *et al* 1978) Of particular interest seems to be the marked vasoconstriction that can be produced in the mesenteric (Ferrer *et al.* 1965) and coronary (de Mots *et al.* 1978) vascular beds in man. Clinical reports suggest that digitalization of elderly patients implies a risk of acute hemorrhage and necrosis of the intestine because of vasoconstriction in the mesenteric circulation (Gazes *et al* 1961 Muggia 1967 Kyrelels & Kraft 1970). However in many of these cases the pre-existing conditions make the contribution of cardiac glycosides difficult to assess.

The clinical consequences of digitalis-induced vasoconstriction and increase in afterload, seem to be of particular importance in patients with acute CHF as it has been shown that the vascular effects are immediate and distinctly precede the inotropic action of these drugs (Schenz *et al.* 1977) Digitalization has in some cases been associated with a hypertensive response causing clinical complications such as pulmonary edema (Ahmed *et al* 1950, Bayliss *et al* 1950 Cohn *et al.* 1969 Kumar *et al.* 1973) However it is possible that some of these vascular reactions can be avoided by slow injection of the drugs (de Mots *et al* 1978) In dogs, a reduced myocardial blood flow has been reported after both acute and chronic digitalization (Steiness *et al.* 1978). Whether such effects may have any clinical implications is unclear

2 Diuretics

In patients with acute CHF a rapidly acting diuretic like furosemide relieves pulmonary congestion by two actions It was shown that on i.v injection of the drug, there was a significant decrease in left ventricular end diastolic pressure immediately after the administration (Dikshit *et al* 1973 Piepenbrock *et al.* 1977). This can probably be attributed to an increase in peripheral venous capacitance Thus, Dikshit *et al* (1973) demonstrated a significant decrease in left ventricular filling pressure accompanied by an increase in calf venous capacitance within 5–15 minutes after the administration. This action was not related to the diuretic properties of the drug, as peak increase in urine flow occurred at 30 min and peak natriuretic effect after 60 min The vascular effects of furosemide were considered to be of considerable therapeutic significance (Piepenbrock *et al.* 1977). Also ethacrynic acid (Kim *et al.* 1971) and bumetanide (Brogden *et al.* 1975) have been reported to be effective in acute CHF However ethacrynic acid failed to exhibit any direct vascular effect (Schenk *et al* 1975). On the other hand such an action has been demonstrated for bumetanide (Mack *et al* 1980, Steward *et al.* 1980)

Mond *et al* (1974) investigated patients with suspec

ted acute myocardial infarction receiving furosemide. They found significant falls in CO stroke volume, pulmonary artery and pulmonary arterial wedge pressures, together with a significant rise in the peripheral vascular resistance 30–60 minutes after administration These changes were most probably produced by a decrease in intravascular volume caused by diuresis. It has been stressed that if left ventricular volume is excessively reduced a substantial decrease in CO may occur leading to hypotension and shock

It has been shown that diuretic therapy for CHF could be used alone on a chronic basis (Rader *et al* 1964 McHaffie *et al* 1978). McHaffie *et al* (1978) showed in six patients with CHF and sinus rhythm that oral furosemide controlled the symptoms and that addition of digoxin did not further improve the condition. On basis of their results they suggested that diuretics could be used as drugs of first choice for some patients with heart failure and sinus rhythm It is known that long term diuretic therapy decreases peripheral resistance. It cannot be excluded that this action is of importance when diuretics are used as the sole treatment of CHF

Continuous diuretic treatment will lead to hyperaldosteronism (Nicholls *et al* 1974). Use of an aldosterone antagonist combined with a thiazide diuretic or if CHF is severe, use of a loop diuretic instead of the thiazide has therefore been suggested (Davis & Wilson 1975).

3 Other drugs

A Morphine In a recent review on the treatment of CHF (Forrester & Waters 1978) morphine was considered "perhaps the most important agent used in the treatment of acute pulmonary edema" The beneficial effect of morphine in this condition is probably due to several factors (Grendahl *et al* 1973). Morphine reduces anxiety and tension in the patients contributing to a decrease in oxygen consumption It has a respiratory depressant effect which may be of value because the forced respiration in acute pulmonary edema probably leads to great fluctuations in intrathoracic pressure, promoting transsudation into the alveoli Because of the depressive action on the respiration it has been recommended that morphine should always be accompanied by administration of oxygen (Ru… & Abelmann 1974)

Morphine often causes a slight fall in systolic … pressure (Grendahl *et al* 1973 Gould *et al.* 197… a fall in tension-time index and left ventricular … This is, however not a consistent finding (Le… *et al* 1978)

Morphine also produces a peripheral venous … arteriolar dilatation probably by a reflex decrease … sympathetic alpha-adrenoceptor mediated tone (Ze… *et al* 1974) Pooling of venous blood has been demonstrated both in dog (Henney *et al* 1966, Ward … *al* 1972) and in man (Kayan *et al* 1966). Howe… Zelis *et al* (1974) showed this effect to be small … found it difficult to explain the marked clinical im… provement in pulmonary edema after administration of morphine by the peripheral venodilator action alo… This view is supported by the findings of Timms … *al* (1980) who stressed the importance of the effe… of morphine on the central nervous system in … condition.

In dogs morphine was found to have a posit… inotropic action attributed to a release of catech… amines from the adrenal medulla (Vasko *et al* 19… However an increase in contractility was found … after adrenalectomy (Vatner *et al* 1975). It was … shown that morphine induced a significant corona… vasoconstriction in the unanaesthetized dog (Va… *et al* 1975). In man no positive inotropic effect … morphine has been demonstrated (Wang *et al* 19… *Lee et al 1976, Gould et al 1978), and rather a…* crease in coronary blood flow (Leaman *et al* 197…

Generally the hemodynamic effects of intraveno… morphine are small even if hypotension has been … ported in some patients with acute myocardial infar… tion (Thomas *et al* 1965).

B Theophylline Theophylline (aminophylli… given intravenously has for a long term been us… in the treatment of acute CHF Theoretically the c… diovascular effects of the drug may motivate th…

Theophylline has a well established ability to … crease the contractility of the myocardium (see, … Kukovetz & Pöch 1969 Andersson & Persson 19… Its mode of action has not been established, but po… sibly part of its positive inotropic action is mediat…

via release of catecholamines. Supporting such a view theophylline increases the urinary excretion of noradrenaline and adrenaline in man (Atuk et al. 1967). The increase in contractility may also be linked to an increased influx of calcium in the myocardial cell excitation (Scholz & Reuter 1976, Beresewicz & Reuter 1977) and to the ability of theophylline to inhibit phosphodiesterase (Dönges et al. 1977, Korth 1978). The positive inotropic effect of theophylline is added to that of noradrenaline (Rall & West 1963), glucagon (Marcus et al. 1971), and ouabain (Strubelt & Fiesel 1973).

Clinically theophylline produces consistent increases in CO in patients with cardiac disease and CHF (Parker et al. 1966, Ueda et al. 1967, Hempelmann et al. 1978). The effect on heart rate is often moderate (Parker et al. 1966).

Except for the cerebral circulation, where theophylline has been shown to reduce the blood flow (Wechsler et al. 1950, Skinhøj & Paulson 1970, Magnussen & Hoedt Rasmussen 1977), theophylline has a general vasodilating effect. This can be shown both on the venous (Ogilvie et al. 1977) and arterial (Parker et al. 1967, Hempelmann et al. 1978) side of the circulation. The pulmonary arterial pressure is reduced (Werkö & Lagerlöf 1950, Parker et al. 1966, Hempelmann et al. 1978) most probably due to pulmonary arteriolar dilatation. Coronary flow is increased by direct effect on the coronary vessels (Oes et al. 1977). However measurements in dogs and humans have shown that the increased coronary flow does not improve the oxygen supply to the myocardium, but is rather the result of theophylline increased work of the heart (Foltz et al. 1950, Maxwell et al. 1959, Ito & Hasegawa 1963).

The direct effects of theophylline on the heart and peripheral vessels leading to increased CO and decreased peripheral resistance, often produce an unchanged mean arterial pressure, an increased pulse amplitude and increased flow in several vascular regions. On the other hand, acute hypotensive effects are clinically well known, and so are cardiac arrhythmias. These effects may be deleterious in critically ill patients and preclude the use of the drug (Camarata et al. 1971, Pfeifer & Greenblatt 1978).

In patients with severe CHF the pharmacokinetics of theophylline are changed (Jenne et al. 1974, Hendeles et al. 1977). The apparent volume of distribution is little changed but elimination is delayed. Special care must be taken at repeated dosing.

II. THERAPEUTIC ALTERNATIVES

I. *Inotropic drugs*

The difficulties and risks with cardiac glycosides have encouraged the search for new drugs with clinically positive inotropic properties. A large number of pharmacological agents representing different mechanisms of action has been investigated as possible therapeutic agents in CHF (Table II). Several drugs have been found useful for treatment of acute CHF. Unfortunately most of them have a limited role in chronic treatment.

A. Drugs stimulating adrenoceptors. Although it has been known for several years that drugs stimulating alpha-adrenoceptors can increase cardiac contractile strength (Govier 1967), clinically useful drugs mainly have beta-adrenoceptor stimulating properties. Some of these drugs and their cardiac and peripheral effects are given in Tables III and IV.

Beta-receptor agonists have complex actions on the heart. Their positive inotropic action is thought to be preceded by a stimulation of adenylate cyclase and a resulting increase in cyclic AMP. Cyclic AMP-dependent protein kinases catalyze the phosphorylation

Table II. Therapeutic alternatives to traditional treatment of CHF

1. *Inotropic drugs*
   a) Drugs stimulating adrenoceptors
   b) Phosphodiesterase inhibitors
   c) Glucagon
   d) Other drugs
      amrinone
      AR-L115
2. *Vasodilators*

of proteins that regulate calcium fluxes across the sarcolemma and sarcoplasmic reticulum, and possibly the binding of calcium to the contractile apparatus (Tsien 1977).

Cardiac beta-receptors are generally believed to be of $beta_1$-type. However, Carlsson et al. (1977) showed

that there are both $beta_1$ and $beta_2$ receptors in the heart. Experimentally it was found that $beta_2$ receptor selective agonists like salbutamol and terbutaline had a relatively greater chronotropic than inotropic effect (Farmer *et al* 1970 Carlsson *et al* 1977). Carlsson *et al* (1977) therefore suggested that there are both $beta_1$ and $beta_2$ adrenoceptors in the sinoatrial node and in the ventricular myocardium, but that the relative distribution differs. $Beta_1$ is the predominant type of receptor in both regions, but the $beta_1/beta_2$ concentration ratio is higher in the myocardium than in the sinus node. This hypothesis may explain why some of the beta receptor agonists used in the treatment of heart failure have a more pronounced inotropic than chronotropic effect.

● *Noradrenaline* has a marked positive inotropic effect but increases peripheral resistance by stimulation of vascular alpha-receptors. The vasoconstrictor effect leads to reflex vagal stimulation resulting in only a moderate increase in heart rate. There is a decrease in renal blood flow and in patients with myocardial ischemia arrhythmias can be provoked.

● *Dopamine* has stimulating effects on both alpha- and beta receptors as well as on dopamine receptors in the renal mesenteric, coronary and cerebral vascular beds mediating vasodilatation (see Goldberg *et al.* 1977). Dopamine has a good inotropic effect, mediated partly directly via beta receptors in the myocardium and partly indirectly by release of noradrenaline from sympathetic nerve terminals. The noradrenaline releasing effect is thought to be responsible for the arrhythmias that can be provoked with the drug. The chronotropic effect of dopamine is moderate.

Dopamine has dose related hemodynamic effects in man. In low doses (infusion rates 2–5 μg/min) there is an increase in CO and renal blood flow with little increase in heart rate and either reduction or no change in total peripheral resistance. With increasing doses both blood pressure and peripheral resistance increase, heart rate may not change, but renal blood flow decreases. High doses may cause nausea and vomiting in some patients. In patients needing a marked inotropic support the peripheral effects are dose-limiting unless combined with a vasodilator (Cohn & Francis 1978).

Dopamine has been used with success in refractory CHF in CHF during or after cardiac surgery and in shock (Goldberg *et al* 1977).

● *Dobutamine* is a dopamine derivative with considerably more pronounced effects on contractility than on heart rate in animal experiments (Tuttle & Mills 1975). In contrast to dopamine, dobutamine does not act on dopamine receptors (Robie & Goldberg 1979), has no renal vasodilating activity and does not possess any noradrenaline releasing effect (Robie *et al.* 1974). The predominant inotropic effect can thus be obtained without undue tachycardia or arrhythmias. Dobutamine has, compared with noradrenaline, a relatively weak effect on vascular alpha- and beta-receptors (Robie *et al* 1974).

Hemodynamic studies in man have demonstrated that dobutamine causes dose releated increments of CO in patients with varying degrees of CHF (see Goldberg *et al.* 1977). Some clinical studies have shown that dobutamine was superior to both isoprenaline and dopamine for the treatment of CHF (Kersting *et al.*

Table III Cardiac effects of adrenoceptor agonists.

	Inotropic effect	Chronotropic effect	Arrhytmogenic action
Noradrenaline	++	+	++
Dopamine	++	+(+)	+(+)
Dobutamine	++	+	–
Isoprenaline	++	+++	++
Prenalterol	++	+	–
Salbutamol	+(+)	++	–

Table IV Peripheral effects of adrenoceptor agonists

	Pheripheral resistance	Renal blood flow	Receptor effect	
			alpha	beta
Noradrenaline	∣	∣	+++	
Dopamine	–(∣)	∣(∣)	+(+)	+
Dobutamine	–(∣)		+	+(+)
Isoprenaline	∣	∣	–	++
Prenalterol	–(∣)			(+)
Salbutamol	∣			++

1976 Loeb *et al.* 1977 Stoner *et al.* 1977 Sakamoto & Yamada 1977). Dobutamine has been shown not to increase heart rate even when given in doses that produce a prominent increase in myocardial contractility (Akhtar *et al.* 1975). However, in patients with myocardial infarction dobutamine causes a significant increase in heart rate limiting its usefulness in patients with recent myocardial infarction (Rehnqvist & Lundman 1979). In children with CHF dobutamine was found to be effective in augmenting cardiovascular function (Driscoll *et al.* 1979).

Dobutamine is generally well tolerated, transient nausea and vomiting have been reported (Andy *et al.* 1977) and also ventricular arrhythmias (see Goldberg *et al.* 1977, Rehnqvist & Lundman 1979).

Mikulic *et al.* (1977) compared the hemodynamic effects of dobutamine and nitroprusside in patients with severe CHF. They found that both drugs increased CO and decreased pulmonary vascular resistance. Heart rate showed little changes. Evidence was presented indicating that the decrease in peripheral vascular resistance during dobutamine infusion was a manifestation of a reflex decrease in systemic vascular resistance.

In combination with nitroprusside dobutamine seems to be the most potent pharmacological means available for restoring CO to adequate levels in severe pump failure (Cohn & Franciosa 1978).

● *Isoprenaline* is the most potent of the available drugs producing a marked inotropic effect together with pronounced tachycardia. The drug has no effect on alpha-receptors in doses used clinically, and the effects on $beta_1$- and $beta_2$-receptors are about equal. Clinically there is an increase in renal blood flow, a decrease in diastolic blood pressure, and, in myocardial ischemia, a strong tendency to produce arrhythmias.

It cannot be excluded that part of the chronotropic action is caused by the $beta_2$-receptor stimulating properties of the drug inducing peripheral vasodilation as well as cardiac stimulation.

● *Prenalterol* (H 133/22, the (–) isomer of H 80/62) is a selective $beta_1$-receptor agonist. Studies in animals have shown that prenalterol has no alpha-receptor stimulating properties (Carlsson *et al.* 1977, Hedberg 1980) and it has only minor chronotropic effects in doses sufficient to produce an inotropic response. Scott *et al.* (1979) found that in normal man prenalterol given i.v. increased CO mainly due to an increase in stroke volume as there was little change in heart rate. Mean arterial pressure showed little change but pulse pressure increased. Peripheral resistance fell significantly. Rönn *et al.* (1980) suggested this effect partly explainable by an effect on vascular $beta_1$-receptors, as animal experiments have indicated the presence of such receptors in some vascular beds.

Prenalterol's tendency to produce arrhythmias seems to be low and similar to that of dobutamine. Kraus *et al.* (1978) studying the racemate H 80/62 given orally to healthy volunteers found a dose-related increase in myocardial contractility. Thus, prenalterol is orally active and may offer an interesting alternative to digitalis in long-term treatment.

● *Salbutamol.* Salbutamol is a selective $beta_2$-receptor agonist widely used in the treatment of chronic obstructive lung disease. Animal experiments have shown that salbutamol has inotropic and chronotropic effects, increasing heart rate more than contractility (Farmer *et al.* 1970, Lumley & Broadley 1977). Its maximum effect on tension in isolated guinea-pig atria was about one third of that of isoprenaline. Salbutamol is also a potent vasodilator (Cullum *et al.* 1969). The hemodynamic effects of salbutamol have been studied in patients with various cardiac disorders, including acute myocardial infarction (Lal *et al.* 1972), mitral valve disease (Gibson & Coltart 1971), after cardiac surgery (Poole-Wilson *et al.* 1977), congestive cardiomyopathy (Sharma & Goodwin 1978), and in patients with chronic CHF (Bourdillon *et al.* 1980). In the latter patients Bourdillon *et al.* (1980) found that cardiac index increased, systemic vascular resistance and pulmonary artery and end-diastolic pressures fell, and there was a 10 % increase in heart rate. Similar results were obtained after i.v. and oral administration. The authors suggested the effects attributable mainly to a decrease in afterload caused by vasodilatation and concluded that salbutamol was a useful drug in the treatment of CHF. They also, however, reported on oral treatment (4 mg q.d.s.) for more than two months in patients with severe CHF in whom no objective evidence of improvement was observed.

B. Phosphodiesterase inhibitors. Many drugs can be characterized as phosphodiesterase inhibitors. Among the best known are the methylxanthines, e.g. theophylline and caffeine. The inotropic effects of the methylxanthines have been known since many years (see e.g. Plavec 1908). However so far it has not been settled what relations exist between this effect and the ability of the drugs to inhibit phosphodiesterase and increase the intracellular concentration of cyclic AMP (Tsien 1977). Thus, papaverine, which is 10–1 000 times more potent as a phosphodiesterase inhibitor than theophylline (Amer *et al* 1975) produces no positive inotropic effect (Henry *et al* 1975) despite almost 100 % increase in cyclic AMP levels. Properties of the phosphodiesterase inhibitors other than their ability to inhibit phosphodiesterase may be the main factors determining whether or not the drug will possess a positive inotropic affect.

Besides theophylline several other drugs characterized as phosphodiesterase inhibitors have been tested in patients with CHF Among these is *UK 14,275* In animals, this drug given i v produced dose related significant increases in CO and peak left ventricular dp/dt (Follath *et al* 1976). Large doses produced a fall in blood pressure and an increase in heart rate. Inotropic effects could also be demonstrated in man (Follath *et al* 1976 Jackson *et al* 1978). Thus Jackson *et al* (1978) in healthy volunteers found that *UK 14 275* given intravenously had a significant inotropic activity as judged by shortening of the preejection period *UK 14,275* was without any significant chronotropic activity and seemed to be a less potent inotropic drug than the catecholamines. The effect was lost after beta receptor blockade.

In patients with coronary artery disease the positive inotropic action of *UK 14,275* was confirmed There was no accompanying increase in heart rate, and peripheral resistance decreased significantly (Jewitt *et al* 1978). The drug produced a prolongation of the Q–T interval and therefore its potential arrhythmogenicity requires evaluation (Jewitt *et al* 1978). Whether this drug, which seems to be effective at oral administration may provide an alternative to digitalis remains to be established.

C Glucagon has been shown to improve cardiac performance in both experimental animals (Farah & Tuttle 1966) and in human volunteers (Parmley *et al* 1968). The mechanism of action of glucagon is thought to be an activation of adenylate cyclase independent of the beta receptor and consequent increase in cyclic AMP There is however disagreement of whether or not changes in cyclic AMP are necessary for the positive inotropic effect of glucagon (Henry *et al* 1975

Although a positive inotropic effect of glucagon in man has been demonstrated (Linhart *et al.* 1968, Williams *et al* 1969), the results in patients with acute and chronic CHF have not been consistent, but rather discouraging (Amsterdam *et al* 1970 Vander Ark & Reynolds 1970). Goldstein *et al* (1971) found that papillary muscles from patients with chronic cardiac failure were uniformly associated with complete loss of the normal enhancement of contractility and associated activation of adenylate cyclase after glucagon They suggested this to be the explanation of the inefficacy of the drug in the treatment of patients with chronic CHF

D Other drugs. Amrinone, has recently been shown to increase myocardial contractility both *in vitro* and *in vivo* in animals. In dogs it increased CO without reducing ventricular filling pressures. Neither heart rate nor arterial pressure were significantly altered and no arrhythmias were produced (Farah & Alousi 1978. Also a direct vasodilating effect of the drug has been demonstrated (Millard *et al* 1980). The mechanism of action of the drug is unknown but different from that of cardiac glycosides, catecholamines and phosphodiesterase inhibitors. In normal man a positive inotropic effect was shown (de Guzman *et al* 1978) Such an action was confirmed in patients with CHF already receiving full doses of digitalis (Benotti *et al* 1978. There were significant increases in cardiac index and peak rate of left ventricular pressure rise and decrease in left ventricular end-diastolic pulmonary-capillary and right atrial pressures. Mean heart rate was unchanged and there was a non-significant decrease in aortic mean pressure Similar findings were done by Le Jemtel *et al* (1979) Oral amrinone was also effective and acutely improved left ventricular performance in patients with advanced CHF that persisted despite treatment with digitalis, diuretic drugs and after-load reducing agents (Wynne *et al* 1980). The effect seemed to persist during long-term treatment, but

o of nine patients treated chronically developed ombocytopenia that resolved after amrinone administration was discontinued.

Amrinone seems to be a most promising inotropic drug. However the possible serious adverse reactions evoked by the drug has to be evaluated before long term treatment can be recommended.

AR-L115 is another interesting drug said to have marked inotropic action and a mechanism of action different from that of cardiac glycosides and catecholamines. It is not related to amrinone (Thormann *et al* 1980). Preliminary data showed that in patients with congestive cardiomyopathy AR L115 given both i.v. and orally could mobilize contractile reserve in the hospitalized heart (Thormann *et al* 1980).

Even if neither amrinone nor AR L115 will develop into clinically useful drugs, they may serve as tools for elucidation of new approaches to increase the cardiac contractility.

2 Vasodilators

During the last decade, growing interest has been given to "unloading" of the myocardium by means of vasodilators as a therapeutic principle in CHF. The drugs commonly used for this purpose, their clinical application, and their effectiveness have been reviewed extensively (see e.g. Chatterjee *et al.* 1973, Cohn & Franciosa 1977, Mason 1978, Chatterjee & Parmley 1980).

To use these potent drugs optimally and with acceptable risks, detailed knowledge about their modes of action and their pharmacokinetics in different disease states is desirable. Unfortunately, for many of them information on these points is lacking.

Common to all vasodilators is their ability to reduce tone of vascular smooth muscle with no or little effect on the myocardium. This can be achieved indirectly by decreasing the amounts of vasoconstrictive substances in the vicinity of the smooth muscle cell, or directly by interfering with the different steps linking excitation and contraction in the muscle cell.

Johansson (1978) described the vascular smooth muscle cell as a black box receiving a great number of impulses, exemplifying the many intrinsic factors regulating tone in vivo. Among these are nervous influences, effects of circulating and "local" hormones, and physicochemical factors (Figure 2). As a net result the black box produces a mechanical response: contraction or relaxation.

The contractile machinery of the vascular smooth muscle cell, like in myocardium and skeletal muscle, consists of actin and myosin filaments, whose degree of overlap determines the contractile tension produced by the cell. The interaction between actin and myosin is energy consuming and it is regulated by the concentration of ionized calcium available to the contractile proteins. This concentration is a net result of supply and removal. There are two main sources of activator calcium: influx of extracellular calcium through the plasma membrane, and release of calcium from intracellular stores, mainly the sarcoplasmic reticulum and possibly the mitochondria. Corresponding mechanisms of removal of calcium from the contractile proteins would be extrusion through the plasma membrane and re-uptake into intracellular stores (Figure 3 and 4) (next page).

There are reasons to believe that myogenous spontaneous tone and also vasomotor responses to extrinsic stimuli are mediated in some blood vessels by electrical responses of the smooth muscle cell membrane – electro-mechanical coupling. Action potentials are elicited where the inward current, at least in part is carried by calcium (Figure 3). This calcium influx occurs through specific calcium channels in the membrane – the membrane potential sensitive calcium channels (Bolton 1979). These are opened as the pot

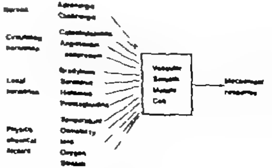

Figure 2. Factors influencing the response of vascular smooth muscle cell (Johansson 1978).

ential across the cell membrane is reduced presumably also in smooth muscle cells that normally do not produce action potentials

Many drugs e.g alpha-adrenoceptor agonists and angiotensin II are believed to promote calcium influx through this channel other drugs e.g. calcium antagonists like verapamil and nifedipine are able to specifically block it

There are also blood vessels e.g. *large elastic* and conduit arteries, but also some arterioles in which some vasoactive agents can cause contraction without associated electrical events – pharmaco-mechanical coupling. Calcium influx may then occur mainly through another type of membrane channel (Figure 4) the "receptor operated calcium channel" (Bolton 1979) whose function is not necessarily dependent on the membrane potential This channel probably also has permeability for ions other than calcium and thus may have importance for its physiological function Calcium antagonists do not block these channels effectively

It is possible that influx of calcium during activation of the cell membrane or release of calcium from a binding site associated with some membrane receptors can cause release of further calcium from intracellular stores, which contributes to the tension produced

It should thus be possible to relax a vascular smooth muscle cell by preventing the inflow and release of calcium either this is done by blocking the receptors *controlling the calcium channels or by blocking se*lectively the calcium channels themselves possibility is to enhance the removal of calcium from the contractile proteins. It has been shown that the of calcium in the sarcoplasmic reticulum, and the extrusion of calcium through the cell membrane be stimulated by cyclic AMP Accordingly stimulate the formation of cyclic AMP (e.g [illegible] adrenoceptor agonists, glucagon) or prevent breakdown *of the nucleotide (e.g. methylxanthines)* can vasodilatation Early studies suggested that cyclic AMP and cyclic GMP would operate as antagonists in the smooth muscle cell – cyclic GMP increasing muscle tone, cyclic AMP reducing it. However, the relaxant effect of nitroglycerin in bovine mesenteric artery is associated with an increase in cyclic GMP levels (Axelsson *et al* 1979). Presently it may be concluded that the role of cyclic GMP in the control of smooth muscle tone is far from settled.

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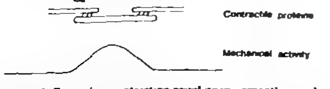

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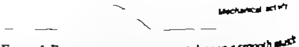

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2.1.1 *Alpha-adrenoceptor blockers.* In patients with CHF part of the increase in systemic vascular resistance is mediated by noradrenaline, released locally or delivered humorally acting on vascular alpha-adrenoceptors. Vasodilatation by means of alpha-receptor blocking drugs therefore seems an attractive approach. There are, however, marked and sometimes clinically significant differences between the alpha-receptor blocking drugs most often used in the treatment of CHF: prazosin, phentolamine and phenoxybenzamine.

It is now established that there are several subgroups of alpha-receptors. The alpha-receptor located on the adrenergic nerve-terminal and involved in the regulation of noradrenaline-release (alpha$_2$) is different from that located postjunctionally in the effector organ (alpha$_1$) (Langer 1974). Besides, there is increasing evidence that the postjunctional alpha-receptors in different organs not necessarily are identical (Harper *et al.* 1978, Drew & Whiting 1979, U'Prichard & Snyder 1979). These differences between alpha-receptors may have therapeutic implications as e.g. selective blockade of certain alpha-receptors ought to be possible. However, many of the present alpha-receptor blockers have actions on other receptor systems.

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There are also blood vessels, e.g. large elastic and conduit arteries but also some arterioles in which some vasoactive agents can cause contraction without associated electrical events – pharmaco-mechanical coupling. Calcium influx may then occur mainly through another type of membrane channel (Figure 4) the "receptor operated calcium channel" (Bolton 1979) whose function is not necessarily dependent on the membrane potential This channel probably also has permeability for ions other than calcium and this may have importance for its physiological function Calcium antagonists do not block these channels effectively

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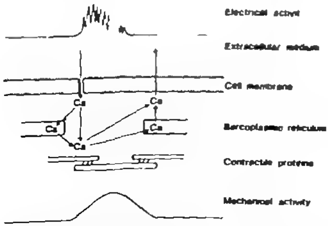

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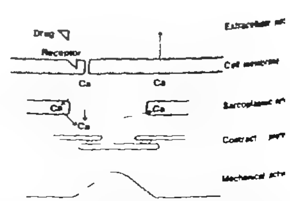

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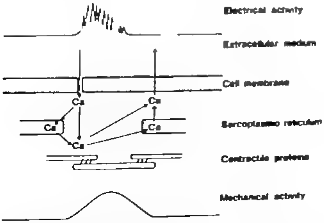

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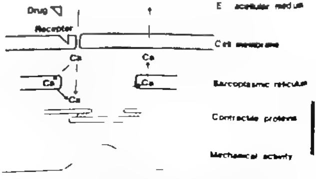

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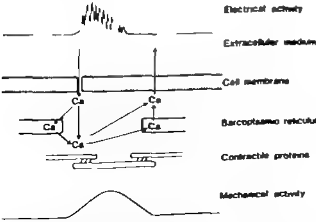

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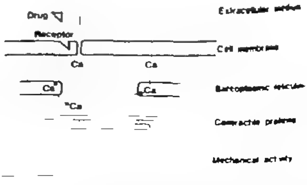

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venous capacitance bed. Practically no effects of the drug has been demonstrated on isolated cardiac muscle (Chatterjee *et al.* 1973, Kreye *et al.* 1975).

The mode of action of nitroprusside has not been elucidated (see e.g. Kreye 1980). Its vasodilator action seems to be a feature of the whole molecule, is independent of extracellular calcium and an interference with transmembrane calcium influx is not necessary. Nitroprusside has not been demonstrated to increase calcium uptake into intracellular stores or to promote active extrusion of calcium (Kreye 1980).

Nitroprusside is an activator of smooth muscle guanylate cyclase and increases the intracellular concentration of cyclic GMP in several smooth muscles; cyclic AMP levels are not affected (Kreye *et al.* 1975, Kreye 1980). Although it is tempting to speculate on a causal relationship between cyclic GMP and the relaxant action of nitroprusside, such a relation has yet to be demonstrated.

A positive finding is that nitroprusside causes a concentration dependent hyperpolarization of some vascular smooth muscles, and this may contribute to its relaxant action.

● *Nitroglycerin and nitrates* are effective smooth muscle relaxants. Nevertheless, their cellular mode of action has not been elucidated. It is believed that nitroglycerin acts on specific nitrate receptors in the vascular smooth muscle wall. By reacting with sulfhydryl groups at the receptor the active nitrate molecule is reduced, releases nitrite ion and thus initiates relaxation of the smooth muscle cell (Nickerson 1975). How this is accomplished is not known. Axelsson *et al.* (1979) found a close correlation between increased intracellular levels of cyclic GMP after treatment with nitroglycerin and relaxation of bovine mesenteric artery. They had no explanation how the increased cyclic AMP level caused muscle relaxation.

It is well known that nitroglycerin has its main effect on capacitance vessels and relatively minor effect on resistance vessels. It has more pronounced actions on large arteries than on small ones, and has little effect on precapillary sphincters. The differences in reaction are difficult to explain but may reflect differences in modes of activation between different vascular regions.

Regardless of its mode of action, the clinical effectiveness of nitroglycerin and nitrates in the treatment of CHF is well documented (see e.g. Abrahams 1979, Chatterjee & Parmley 1980).

● *Hydralazine.* In contrast to nitroglycerin, hydralazine causes relaxation of vascular smooth muscle predominantly in the precapillary arteriolar resistance bed; relaxation of the capacitance vessels is much less pronounced.

However, the effect on resistance vessels is neither uniform nor of equal magnitude in all peripheral vascular beds, being more pronounced in the coronary, renal, splanchnic and cerebral beds than in those in the skin and skeletal muscle (see Taylor 1980).

The cellular mode of action of hydralazine is not known. Studies *in vitro* and *in vivo* in animals exposed to ^{14}C-labelled hydralazine indicated that hydralazine, or active metabolites are tightly bound to the vessel wall (Perry *et al.* 1962, Wagner 1973), but so far it has not been elucidated how the relaxant action is produced. The relaxant potency of dihydralazine on isolated human vessels was low (Lederballe-Pedersen *et al.* 1979). Recent studies (Barron *et al.* 1977, McLean *et al.* 1978) have suggested that hydralazine and its hydrazone derivatives produce effects on vascular smooth muscle both by interaction with the fluxes of calcium from the extracellular medium and by effects on release from intracellular stores.

Clinically the effects of hydralazine lead to an increase in CO in patients with chronic CHF (see Chatterjee & Parmley 1980). It has been discussed whether hydralazine in addition to its vascular effects also has a positive inotropic action contributing to this effect (Khatri *et al.* 1977). Such an action has been demonstrated in isolated papillary muscle but only at a very high dosage making the clinical significance of the finding doubtful.

● *Diazoxide and minoxidil.* Among vasodilators having an effect mainly on arterioles, the antihypertensive drugs diazoxide and minoxidil have had a limited use in the treatment of CHF. Neither for diazoxide (Scriabine 1980) nor for minoxidil (Du Charme & Zins 1980) have the precise mechanism responsible for the relaxation of arterial smooth muscle been defined. Available evidence seems to indicate that diazoxide acts primarily at the cell membrane and inhibits the membrane potential dependent component of excita-

tensive patients this seems to be no problem (Brogden *et al* 1977). In patients with CHF however tolerance development has been reported by several authors (Arnold *et al* 1979 Elkayam *et al* 1979 Packer *et al* 1979).

The mechanism of tolerance development for prazosin remains to be elucidated but it cannot be excluded that changes in the vascular alpha-receptors caused by the disease may contribute. There appears to be no simple pharmacokinetic explanation e.g. inadequate plasma concentrations of the drug (Arnold *et al* 1979).

● *Trimazosin* This is another alpha-receptor blocker with a profile of action similar to that of prazosin (Vlachis *et al* 1975 Franciosa & Cohn 1978 Weber *et al* 1980).

It should be mentioned that several drugs usually not classified as alpha adrenoceptors antagonists have clinically important and sometimes useful effects on alpha receptors.

● *Chlorpromazine is one of these drugs which also has* been used in the treatment of CHF (Elkayam *et al* 1977 Romano & Gulio 1980)

Among vasodilators "directly" acting drugs is a term often used for agents whose site of action is believed to be the cell membrane or intracellular affecting calcium fluxes or enzymatic processes involved in the delivery of energy needed for contractile activity. They all antagonize the vasoconstrictor effects of various endogenous substances including noradrenaline, serotonin, angiotensin II and potassium. Among these drugs are calcium antagonists, sodium nitroprusside nitroglycerin and nitrates hydralazine diazoxide and minoxidil. The mechanisms of action of these drugs at the cellular or biochemical level are often poorly understood but are not identical

● *Calcium-antagonists.* From a theoretical point of view vasoconstriction obtained by blockade of a mechanism that is common to all factors contributing to the increased systemic vascular resistance in CHF is attractive. Calcium influx through the cell membrane seems to be an important step in the action of many contractant agents. Several drugs have been characterized as calcium antagonists; their main action is believed to be blockade of calcium influx in smooth muscle (Fleckenstein 1977). However actions on steps coming later in the sequence of processes linking excitation to contraction, cannot be excluded (Zsoter 1980).

All calcium antagonists have a negative inotropic action on the heart (Fleckenstein 1977) and some of them e.g. verapamil has marked effects on AV-conduction. These actions cannot be regarded as favorable in the treatment of CHF. Among the calcium antagonists, however nifedipine has relatively pronounced effects on peripheral vessels than on myocardium and AV-conduction. Studies on isolated human vessels have demonstrated a relaxant effect on both arteries and veins (Mikkelsen *et al.* 1978, 1979c). However in patients the effects on the arterial side of the circulation seem to be predominant (Mostbeck *et al* 1975 Simonsen & Nitter Hauge 1978 Koch 1980) leading to a decrease in afterload. On the other hand an effect on the venous side cannot be excluded, as a reduction of the filling pressures of the ventricles can be demonstrated in patients in whom they are increased (Polese *et al* 1979 Koch 1980).

The experience of using nifedipine in the treatment of CHF is limited. In patients with acute pulmonary edema, the drug was effective (Polese *et al* 1977). Recent studies on the hemodynamic actions in patients with chronic CHF also indicate beneficial effects (Klugmann *et al* 1980 Matsumoto *et al* 1980)

● *Sodium nitroprusside* The clinical effectiveness of sodium nitroprusside in acute heart failure is well documented (see e.g. Chatterjee *et al* 1979). *In vitro*, the drug is a general smooth muscle relaxant but considerable differences between various smooth muscle preparations have been demonstrated. Tonic smooth muscle, e.g tracheal and most vascular smooth muscle is highly responsive to the drug, whereas phasic smooth muscle, e g uterus and vas deferens from rat is practically unresponsive (Kreye *et al* 1975). Golenhofen (1976) found that in smooth muscle exhibiting both tonic and phasic contractile properties, nitroprusside selectively interfered with the tonic part of the contraction whereas calcium antagonists like verapamil and nifedipine inhibited the phasic component.

In isolated vascular smooth muscle nitroprusside has a relaxant action, regardless of the agent used for contraction (see Kreye 1980). It causes relaxation also *in vivo* of both the arteriolar resistance vessels and the

Both the therapeutic principles "stimulation" and "unloading" of the heart have proved to be clinically useful applied alone or in combination. Further clinical experience is needed to establish the place of these principles in the treatment of CHF

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tion-contraction coupling (Rhoades & Sutter 1971), i e. mainly a calcium antagonistic effect of the drug.

● *Prostaglandins and prostacyclin* The vasodilator properties of some prostaglandins and prostacyclin (Szczeklik *et al* 1980) make these drugs promising alternatives in some patients with CHF So far they have only been used to a limited extent but preliminary results seem positive (Awan *et al* 1980)

● *Captopril* Contributing to the elevated systemic vascular resistance found in patients with CHF and low CO might be increased blood levels of angiotensin II It should therefore be expected that inhibition of the receptor effects of angiotensin II or of the formation of the peptide would be of benefit for at least some patients with CHF Initial experiments with intravenously administered saralasin a competitive angiotensin II antagonist (Gavras *et al* 1977) and teprotide (Curtiss *et al* 1979 Gavras *et al* 1979) an inhibitor of the angiotensin converting enzyme showed that these drugs could improve cardiac function in patients with CHF Captopril which also inhibits angiotensin II converting enzyme can be given orally and has been the preferred drug in the treatment of CHF

It is commonly agreed that angiotensin II has an action preferably on precapillary resistance vessels, veins and capacitance vessels being relatively insensitive (Haddy *et al* 1962 Rose *et al* 1962). However the hemodynamic effects of captopril in patients with CHF suggest effects on both the arterial and venous side of the circulation (Gavras *et al* 1979 Turini *et al* 1979 Ader *et al* 1980 Dzau *et al* 1980). The venous effects of captopril have been explained in several ways (see Chatterjee & Parmley 1980). During treatment, there is a decrease in the levels of circulating noradrenaline (Curtiss *et al.* 1979 Gavras *et al* 1979 Turini *et al* 1979). Captopril also inhibits the degration of bradykinin (Figure 5). It cannot be excluded that captopril's inhibiting effects on the degradation of this vasodilator may play a role (Rubin & Antonaccio 1980), even if no increased plasma levels of bradykinin have been demonstrated (Dzau *et al* 1980). The inhibiting effects on aldosterone release may be a factor of importance. However direct effects of captopril on the vascular smooth muscle seem to be excluded (Rubin *et al* 1978).

"STIMULATION" CONTRA UNLOADING

In 1973 Katz suggested the possibility that i with CHF a reduction in myocardial contractiq compensatory in that it prolongs life by easi burden of the chronically overloaded heart He t raised reservations about the potential utility of powerful inotropic agent in the treatment of ch CHF He based these reservations on the fac there is a paucity of energy reserves in the fum and the balance between energy production energy utilization may be jeopardized in the throphied, chronically overloaded myocardium (1978) further suggested that the lack of chemica ergy may be responsible for myocardial cell death fibrosis in the heart of patients with h failure. Therefore, administration of powerful i ic drugs although causing a temporary impro in cardiac contractile performance may do so a expense of accelerating myocardial cell death

If these speculations are correct, use of vasodi would be more attractive being "a physiologica proach to the treatment of heart failure" (Braun 1977). However use of potent vasodilator drugs ca be expected to be without problems, and even i sodilator therapy obviously has a great therapeu ential it would seem premature to generally r mend vasodilators in place of digitalis. At prese sodilator drugs have a definite role in the manage of patients with refractory CHF but i probably be used more widely also in less se ill patients.

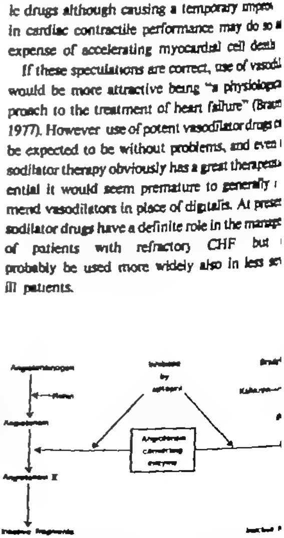

Figure 5 Effects of captopril of possible importance vasodilator actions

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DISCUSSION

Digitalis and vasodilation

Johansson

Back in the thirties Sir James McKenzie argued that the main effect of digitalis was venodilation Does it exist and how important is it for the effect of digitalis?

Andersson.

Digitalis has been shown to have some veno-dilator action in patients with CHF By improving cardiac contractility and increasing CO digitalis reduces symphathetic tone which leads to a vasodilatation both on the arterial and venous side of the circulation. Thus, this is not a direct venodilating effect In fact digitalis contracts isolated human peripheral veins by a direct action and also potentiates contractions induced by noradrenaline.

Calcium antagonists

Cohn

You divided the calcium channels into receptor operated and non receptor operated channels, and suggested that calcium entry blockers such as nifedipine act exclusively on the non-receptor mechanism It has been my impression that the calcium entry blockers attenuate noradrenaline vasoconstriction as well I wonder what your comment is about that?

Andersson.

Noradrenaline is considered to induce vasoconstriction by two mechanisms. One is by increasing calcium inflow and one is by releasing intracellularly bound calcium. In vitro calcium entry blockers like nifedipine do not completely inhibit noradrenaline induced contraction. This may be due to the fact that these drugs do not prevent calcium inflow through receptor operated calcium channels or by their inability to inhibit the intracellular effects of noradrenaline.

Cohn:

I think there seems to be a move at present to become a little less specific about the mechanism of calcium entry. The new terminology for these drugs is calcium entry blockers rather than calcium channel blockers, reflecting perhaps some scepticism about the specificity of the channels.

Andersson.

I think there is a little confusion in terminology. We use the terms calcium antagonists, calcium blockers, calcium channel blockers and now calcium entry blockers. I think that the most practical way to classify these drugs is that of Fleckenstein (1977), measuring their effect on the inward slow calcium current in myocardial cells by voltage clamp. I think that calcium entry blockers is a term as vague as calcium antagonists. I also think that if we use terms to classify drugs without considering their specificity and selectivity in preventing calcium inflow there will be little meaning in talking about them as a specific group of drugs.

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PATHOPHYSIOLOGICAL CONSIDERATIONS IN SELECTING VASODILATOR THERAPY FOR CHF

Jay N. Cohn

The demonstration that vasodilator drugs improve function of the failing left ventricle (Cohn 1973) has provided physicians with a new pharmacological approach to the management of congestive heart failure (CHF). This new approach carries with it, however, responsibility to gain an understanding of the differences in circulatory effects of a wide variety of drugs identified as vasodilators and an understanding of how these different cardiovascular effects may influence the hemodynamic and clinical response to therapy in CHF.

The pharmacodynamic effects that must be considered in selecting a vasodilator drug include its effect on systemic veins versus arteries, its effect on the pulmonary vascular bed, its relative effect on various regional systemic vascular beds, its tendency to produce reflex activation of the sympathetic nervous system, and its direct effect if any on the heart. Factors relating to the patient that need to be considered include the etiology of the heart disease, the severity of left ventricular dysfunction, the magnitude of left ventricular dilation, the compliance characteristics of the left ventricle, and the systemic vascular resistance and resultant arterial pressure. Although our state of knowledge does not yet allow us to utilize all of this information in making a rational decision about whom to treat and which agent to use, it is nonetheless likely that each of these circulatory and pathophysiologic factors has an influence on the systemic and regional hemodynamic response to these drugs and perhaps also on the effect of the therapy on the natural history of the disease. Furthermore, accumulating evidence relating to the mechanism by which the peripheral vasculature becomes constricted in patients with CHF (Cohn *et al.* 1979) now makes it necessary to consider the pharmacologic action of each of these drugs in relation to the neurohumoral state of the individual patient.

VENOUS VS. ARTERIAL EFFECTS

The simplest distinction among the various vasodilator drugs is their relative action on arteries and veins (Miller *et al.* 1976). Relaxation of arterial and arteriolar smooth muscle lowers resistance to blood flow and decreases aortic input impedance. By thus reducing resistance to left ventricular ejection, stroke volume (SV) rises and left ventricular ejection fraction is increased. The effects of this vasodilator intervention on blood pressure are usually only modest in patients with CHF since the fall in systemic vascular resistance is counter-balanced by an increase in SV and cardiac output (CO). Relaxation of smooth muscle in venous capacitance vessels redistributes volume from the central to the peripheral bed and thus reduces ventricular volume and filling pressure. Venous relaxation generally reduces CO in normal individuals whose left ventricles are functioning on the sharp ascending limb of the Frank Starling curve but not in patients with CHF in whom the left ventricle functions on a relatively flat Starling curve (Cohn 1973).

Based on these physiological considerations it would be anticipated that drugs which effectively relax the arterial bed would increase CO predominantly, whereas drugs which act selectively on the venous bed would predominantly reduce filling pressures in the right and left ventricles and in the pulmonary vascular bed. Indeed, drugs such as hydralazine and minoxidil produce a striking increase in CO with only a slight fall in pulmonary wedge pressure consistent with their known selective arterial dilating properties (Franciosa *et al.* 1974, 1977). The nitrates, which have a predominant venodilator effect but also produce some relaxation of arterial smooth muscle, produce

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d minoxidil, are particularly prone to produce reflex chycardia whereas those drugs with concomitant ve us dilating effect, sodium nitroprusside and the ni tes, are less so. The present concept is that reflex lease of norepinephrine into the synaptic cleft exerts feedback inhibition of further norepinephrine release virtue of interaction with presynaptic alpha recep- . Alpha blockers such as phentolamine and di- nzylene block this receptor site as well as the post naptic vasoconstrictor alpha receptor and thus allow r continued norepinephrine release that results in n intense reflex sympathetic activation In contrast, razosin appears to have a selective action on the post ynaptic alpha receptor thus leaving the presynaptic ceptor intact to serve its normal feedback inhibiting nction (Langer 1974) Consequently the reflex re- ponse to prazosin in patients with hypertension is ttenuated

In patients with CHF the expected reflex sympa- thetic discharge in response to vasodilator drugs is markedly attenuated (Cohn & Franciosa 1977) Little if any tachycardia results from administration of hy dralazine or minoxidil, and administration of sodium nitroprusside, nitrates or prazosin generally results in a slowing of the heart rate in these patients Several possible mechanisms may account for this altered re sponse to the sympathetic nervous system 1) the sym- pathetic nervous system is already activated in CHF as manifested by the increase in plasma norepinephrine levels This reflex activation may be relaxed when CO and SV rise in response to the vasodilator drug, 2) reflex responses of the aortic and carotid baroreceptors or the low pressure mechanoreceptors may be inhibited in CHF

DIRECT MYOCARDIAL EFFECTS

Since vasodilator drugs increase left ventricular ejec tion fraction and raise SV in patients with CHF the physiologic distinction between a vasodilator drug and a positive inotropic drug is difficult Isolated muscle studies remain the most precise way to identify direct effects of drugs on myocardial contractility but this method suffers from the vagaries of dosage and the absence of an intact nervous system that may influence muscle function. Most vasodilator drugs studied do not significantly affect myocardial contractility In vivo studies have suggested however that hydralazine has some direct myocardial effect possibly through direct catecholamine release (Khatri *et al* 1977). Whether this contributes to the hemodynamic response to this drug is not clear

Another problem is the distinction between inotropic and vasodilator effects of drugs with known inotropic properties. Drugs such as isoproterenol, dobutami- ne, dopamine, and amrinone all appear to have both inotropic and vasodilator properties. The relative contribution of these two pharmacologic effects in the overall hemodynamic response to these drugs in pa- tients with CHF is difficult to assess. Nonetheless, since these two pharmacologic mechanisms are additive in their effect on left ventricular performance, the use of inotropic and vasodilator drugs in combination ap- pears to be the most effective way to treat severe pump failure (M kulic *et al.* 1977).

ETIOLOGY OF CHF

Left ventricular muscle disease (cardiomyopathy) may result from a wide variety of causes, including ischemia, chronic valvular disease, infections, toxins and infil trative processes (Pierpont *et al* 1978). In general the etiology of the myocardial disease appears to have little influence on the hemodynamic response to vasod lator drugs Nonetheless, certain factors relating to etiology must be kept in mind

Coronary artery disease reduces the effective cor onary perfusion pressure distal to atherosclerotic plaques Modest reductions of blood pressure induced by vasodilator drugs may result in critical reduction of this coronary perfusion pressure and aggravation of myocardial ischemia (Schwartz *et al* 1980). Concern regarding the use of vasodilators is particularly ap- propriate in the setting of acute myocardial infarction but also must be considered in patients with chronic CHF in the setting of severe coronary artery disease. Although these latter patients may tolerate low blood pressures remarkably well the possibility of a dele terious effect on myocardial perfusion must be kept in mind

When mitral regurgitation is an important factor in poor CO the vasodilator drugs have a particularly prominent effect since they result in a reduction of regurgitant fraction and an increase in forward fraction

a striking fall in elevated pulmonary capillary pressures and only a slight and inconsistent increase in CO (Franciosa & Cohn 1981).

If one's goal in treatment of CHF is to both augment CO and reduce an elevated filling pressure then drugs which have a balanced arterial and venous effect would be preferable. Such a dual effect occurs during infusion of sodium nitroprusside (Miller *et al* 1976 Guiha *et al* 1974) and can also be demonstrated during the oral administration of prazosin (Awan *et al* 1978) or the administration of combination therapy with hydralazine and isosorbide dinitrate (Pierpont *et al* 1978[a]). A similar hemodynamic response occurs in response to drugs which block the conversion of angiotensin I to angiotensin II (Curtiss *et al* 1978 Levine *et al* 1980).

PULMONARY VASCULAR EFFECTS

The effects of each of the vasodilator drugs on the pulmonary vascular bed has not been well established. This lack of information is due in part to difficulty in separating direct vascular effects on the pulmonary bed from secondary effects induced by a change in left ventricular function. Furthermore, present techniques do not easily allow one to separate pulmonary arterial from pulmonary venous effects. Nonetheless, considerable differences appear to exist between various drugs in their potency on relaxing pulmonary vascular smooth muscle. One manifestation of this difference in pulmonary vascular effect is the influence of the vasodilator drugs on arterial oxygen saturation. Drugs which relax constricted pulmonary vessels are likely to allow perfusion of poorly ventilated areas of the lung and thus precipitate a fall in arterial oxygen tension (Pierpont *et al* 1980[a]). Modest hypoxemia has been reported during infusion of sodium nitrate, nitroprusside and after administration of nitroglycerin or isosorbide dinitrate. These drugs also produce a fall in pulmonary arteriolar resistance suggesting a direct effect on the pulmonary vasculature. In contrast hydralazine has only modest pulmonary vascular effects and does not significantly alter either pulmonary arteriolar resistance or arterial oxygen tension (Pierpont *et al* 1980[a]). Converting enzyme inhibition does appear to relax the pulmonary vascular resistance but has not been associated with a reduction of arterial oxygenation (Vrobel & Cohn 1980). Prazosin also has a pulmonary vasodilator effect presumably through its inhibition of alpha receptors.

REGIONAL VASCULAR EFFECTS

The goal of therapy of CHF is not only to increase CO but more importantly to restore regional blood flow toward normal. Whereas vasodilator drugs may increase CO the distribution of that output to regional vascular beds will be highly dependent upon the direct effects of the drug on regional vascular resistance. Caution must be exercised however in interpreting the acute responses to drug intervention, since these acute effects may not be representative of the changes in flow that could occur during chronic drug therapy of CHF.

The ideal vasodilator drug would reduce the vascular resistance in each of the critical systemic beds and still allow normal reflex control of vascular resistance during exercise and stress. Studies to date suggest that the renal bed generally shares in the increased CO resulting from vasodilator drugs (Pierpont *et al* 1980[b] Cogan *et al* 1980 Leier *et al* 1981). Data are still too fragmentary to identify the specific effects of any of the presently used vasodilator drugs on other regional blood flows, and particularly to determine whether differing acute effects on regional vascular resistance have any influence on the clinical response to chronic drug therapy. Such studies are currently in progress.

REFLEX ACTIVATION OF THE SYMPATHETIC NERVOUS SYSTEM

Administration of a vasodilator drug to normal subjects or patients with hypertension elicits a reflex response of the sympathetic nervous system manifested by tachycardia. This reflex sympathetic discharge also may have an influence on vascular tone in certain regional vascular beds and thus may alter the peripheral distribution of blood flow. The degree to which various vasodilator drugs stimulate reflex sympathetic discharge depends on a number of incompletely understood phenomena, including changes in aortic systolic, diastolic and mean pressure, effects on the venous capacitance vessels, and effects on the compliance of large arteries. The arterial dilators, hydralazine

ave a long-term beneficial effect on myocardial ctility The poor prognosis in patients with CHF it mandatory that a new and more effective ch to therapy be found. It is likely that this ch will combine the use of drugs that improve muscle function and reduce resistance to left ventricular ejection. Proof that this therapy will prolong life as well as improve hemodynamics must await the results of more long term large scale studies

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as well as an increase in total ejection fraction from the left ventricle (Chatterjee *et al* 1973). A similar though quantitatively less dramatic dual effect may be observed in aortic insufficiency (Bolen & Alderman 1976)

Since the physiologic mechanism of impedance reduction therapy is an increase in systolic shortening these drugs have their most beneficial effect when systolic function is impaired In myocardial diseases characterized by restriction to diastolic filling with only modest impairment of systolic function the response to vasodilator drugs may be small

SEVERITY OF LEFT VENTRICULAR DYSFUNCTION

The deleterious effect of impedance on left ventricular performance is directly related to the severity of the left ventricular dysfunction The normal left ventricle regulates its performance to maintain a constant SV against a wide physiologic range of aortic input impedance The more severely damaged the left ventricle the less capable it is to regulate as impedance rises and the greater the consequent fall in left ventricular SV On the basis of these physiologic considerations it is to be expected that the salutary hemodynamic response to vasodilator therapy would be greatest in patients with most severely impaired cardiac function When left ventricular performance is markedly abnormal administration of vasodilator drugs may even result in a paradoxical rise in aortic pressure because of the profound rise in SV as the systemic vascular resistance is reduced

LEFT VENTRICULAR DILATATION

The increase in SV that accompanies vasodilator therapy is accomplished by greater systolic emptying. Therefore the greater the reservoir for enhancing systolic emptying the greater might be expected to be the hemodynamic response to the drug Studies have suggested that response to a drug that reduces aortic impedance is directly related to the enddiastolic ventricular volume. Similarly compliance characteristics of the left ventricle may influence the response to therapy As noted above, in the presence of restrictive disease ventricular volume might be low and the response to vasodilator drugs disappointing Some evidence does suggest that vasodilator drugs may have a direct effect to increase left ventricular compliance and thus to enhance cardiac performance in part by a Frank Starling mechanism (Brodie *et al.* 1977)

SYSTEMIC VASCULAR RESISTANCE AND ARTERIAL PRESSURE

One would expect that the high systemic vascular resistance indicative of a marked systemic vasoconstrictor response to CHF (Cohn *et al* 1979) would enhance the response to vasodilator drugs. Indeed this appears to be true but surprisingly good hemodynamic responses may also be achieved in some patients whose systemic vascular resistance is not very high. Even in modestly hypotensive patients cautious administration of vasodilator drugs may increase CO with only a small further reduction of the already lowered pressure (Cohn & Franciosa 1978) The variability of the response based upon systemic resistance and arterial pressure makes it imprudent to base the decision about the use of vasodilator drugs on either of these hemodynamic or calculated variables

THE FUTURE OF VASODILATOR THERAPY

Rapid clinical application of the early hemodynamic observations of response to vasodilator drugs in CHF is indicative of the wide acceptance this form of therapy has received It is clear that vasodilator drugs have now become a third component of management of the patient with CHF which includes the use of a positive inotropic drug and a diuretic. The ultimate vasodilator drug for this syndrome has yet to be identified. As our understanding of neurohumoral control mechanism becomes more complete it is likely that specific vasodilator interventions will be tailored for specific patients on the basis of the individual's abnormal circulatory state The use of drugs which specifically block the reninangiotensin system, the sympathetic nervous system or the action of vasopressin all may have a potential place in the future management of CHF

The search for new inotropic drugs continues The medical community has been becoming increasingly skeptical of the potency of oral digitalis in the long-term management of CHF A wide variety of new compounds are being investigated to seek a drug which

ave a long-term beneficial effect on myocardial ctility. The poor prognosis in patients with CHF s it mandatory that a new and more effective ach to therapy be found. It is likely that this ach will combine the use of drugs that improve muscle function and reduce resistance to left ventri cular ejection. Proof that this therapy will prolong life as well as improve hemodynamics must await the re sults of more long-term large-scale studies

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HYDRALAZINE IN CHRONIC CHF

Kanu Chatterjee Jean-Lucien Rouleau and Barry M Massie

Hydralazine was introduced in clinical medicine for the treatment of hypertension as early as 1950 (Moyer & Head Hadley 1950), and its role for the management of hypertensive patients is now firmly established That intravenous hydralazine therapy could be useful in improving cardiac performance of patients with hypertensive congestive heart failure (CHF) was recognized almost three decades ago (Judson *et al* 1956) In these patients a decrease in systemic vascular resistance, along with an increase in cardiac output (CO) and stroke volume (SV) was observed. More recent studies have provided confirmation to these earlier observations and have further demonstrated that beneficial hemodynamic effects of hydralazine are also seen in normotensive, or even hypotensive heart failure patients In this review our experience with hydralazine for the management of patients with chronic CHF is summarized

HEMODYNAMIC EFFECTS OF ORAL HYDRALAZINE IN CHRONIC CHF

Hydralazine is potent vasodilator and causes direct relaxation of the smooth muscle in the peripheral vascular bed (Fries *et al* 1953 Ingenito *et al* 1969) The precapillary arteriolar resistance bed is predominantly affected by hydralazine, and the relaxation of the capacitance vessels is much less pronounced (Fries *et al* 1953 Ingenito *et al* 1969 Koch-Weser 1974) Due to its vasodilatory effect on the arteriolar resistance bed, systemic vascular resistance decreases Systemic vascular resistance is a major component of the total resistance against which the left ventricle operates as a pump As an inverse relation exists between left ventricular outflow resistance and its SV a reduction in systemic vascular resistance is likely to cause an increase in left ventricular SV I patients with CHF associated with low CO and elevated systemic vascular resistance, this unloading effect of hydralazine should be particularly beneficial. The hemodynamic effects of oral hydralazine, therefore, were evaluated in a group of patients with severe, chronic CHF and the results are summarized in Figure 1 and Table I (next page) (Chatterjee *et al.* 1976). There were ten patients in this study eight of these patients received 75 mg and the remaining two received 50 mg or oral hy

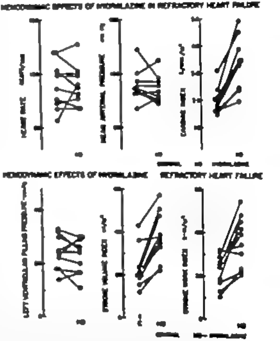

Figure 1 Changes in heart rate, mean arterial pressure, cardiac index (a), left ventricular filling pressure, stroke volume index, and stroke work index (b) after continued hydralazine therapy in ten patients with chronic CHF Average heart rate did not change, although in individual patients some tachycardia was noted Average mean arterial pressure also did not change significantly Cardiac index, stroke volume index, and stroke work index increased in almost all patients. Changes in left ventricular filling pressure were variable (Chatterjee *et al.* 1976)

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Table I Hemodynamic effects of oral hydralazine in patients with refractory CHF (N = 10) (Mean values ± SEM) (Chatterjee & Parmley 1977).

	Control	Hydralazine	p
Heart rate (beats/min)	90±6.9	90±5.8	NS
Arterial pressure (mean) (mm Hg)	89±4.5	85±4.0	NS
Pulmonary arterial pressure (mean) (mm Hg)	37±3.4	38±3.1	NS
Left ventricular filling pressure (mm Hg)	24±2.0	23±2.1	NS
Cardiac index (L/min/m^2)	1.99±0.15	3.39±0.29	<0.001
Stroke volume index (ml/m^2)	23±3.0	38±3.5	<0.001
Stroke work index (g m/m^2)	23±2.4	36±3.7	<0.001
Systemic vascular resistance (dynes sec-cm^{-5})	1748±129	998±115	<0.001
Pulmonary vascular resistance (dynes sec-cm^{-5})	328±54	203±32	<0.001

NS = not significant

dralazine every six hours. The etiology of chronic CHF was ischemic cardiomyopathy in four, cardiomyopathy of unknown cause in four and post valve replacement heart failure in the remaining two. The hemodynamic effects of oral hydralazine in these patients were characterized by a marked increase in CO, SV and stroke work indices along with a decrease in systemic vascular resistance. The changes in mean arterial pressure were variable: in the majority it remained unchanged. In the group as a whole there was no significant change in heart rate, although in occasional patients mild tachycardia was observed. There was no significant change in left or right ventricular filling pressure, however, an increase in CO and SV with little or no change in left ventricular filling pressure indicated improved left ventricular function. Hydralazine induced hemodynamic changes appeared in part related to the dose of administration. The effect of increasing the dose of oral hydralazine on cardiac index in a patient with chronic CHF is illustrated in Figure 2 (Chatterjee *et al* 1979[a]). With the 25 mg dose there was no significant increase in cardiac index. With a 50 mg dose cardiac index increased significantly, and following 75 mg of oral hydralazine there was a further increase in cardiac index. Recent studies indicate that in some patients with severe CHF, 800 to 1200 mg of oral hydralazine per day may be needed to produce beneficial hemodynamic and clinical response (Packer *et al* 1980). With a larger (100 mg) dose of oral hydralazine, a significant decrease in left ventricular filling pressure has also been observed (Franciosa *et al* 1977).

The principal mechanism by which hydralazine improves left ventricular performance in patients with CHF is probably due to the reduction of left ventricular systolic ejection impedance. However, it has been su

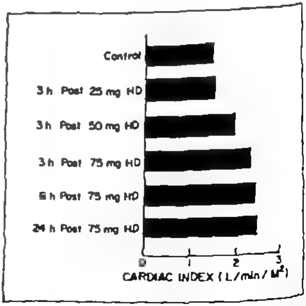

Figure 2 The effect of oral hydralazine on cardiac index in a patient with chronic CHF. With a 25 mg dose, there was no significant increase in cardiac index. With 50 and 75 mg doses, cardiac index increased significantly (Chatterjee *et al* 1978).

gested that hydralazine may have the potential to increase contractile state by a direct, positive inotropic effect. To evaluate the inotropic effect of hydralazine, changes in the force development in isolated papillary muscle preparations were evaluated with increasing concentrations of hydralazine (Figure 3). It is apparent that with a very high concentration there is an increase in the developed force. In clinical practice, however such concentration is not attained, even when a very large dose of hydralazine is used. It appears, therefore, that changes in inotropy play little or no role for enhanced cardiac performance.

COMBINED NITRATE HYDRALAZINE THERAPY

The principal hemodynamic effects of oral hydralazine in patients with chronic heart failure are an increase in CO and a decrease in systemic vascular resistance. In the majority of patients there is little or no change in systemic and pulmonary venous pressure. Elevated left ventricular diastolic pressure and pulmonary venous pressure are common hemodynamic abnormalities in patients with chronic heart failure. A concomitant reduction in pulmonary capillary wedge pressure and left ventricular filling pressure, along with an increase in CO should be beneficial for the management of these patients. With the vasodilators which have a predominant effect on the venous capacitance bed a decrease in pulmonary and systemic venous pressures would be expected. Thus, the hemodynamic effects of combined venodilators (nitrates) and hydralazine were investigated. The hemodynamic effects of nonparenteral nitrates alone, hydralazine alone and combined nitrates and hydralazine therapy were studied in twelve patients with chronic CHF (Figure 4) (Massie et al. 1977). With the use of nitrates or hydralazine or a combination of nitrates and hydralazine, there was no significant change in heart rate or arterial pressure. Nonparenteral nitrates resulted in a significant reduction of right atrial pressure and pulmonary capillary wedge pressure. In addition, there was a small but a significant decrease in pulmonary artery pressure. Nitrates produced no significant changes in cardiac and stroke volume indices, or in systemic or pulmonary vascular resistances. With hydralazine

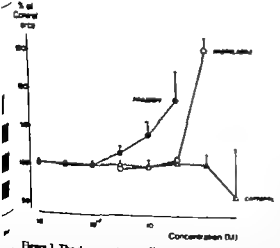

Figure 3. The direct inotropic effects of prazosin, hydralazine and captopril are illustrated. Control measurements of isometric force in groups of cat papillary muscles, studied at lmax at the peak of their length-tension curve, are represented as 100 %. Changes in force with cumulative dose response curves are illustrated for each of the drugs.

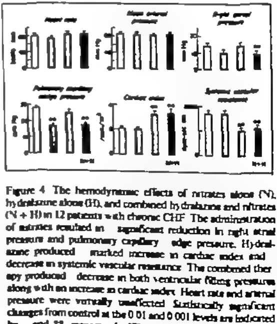

Figure 4. The hemodynamic effects of nitrates alone (N), hydralazine alone (H), and combined hydralazine and nitrates (N + H) in 12 patients with chronic CHF. The administration of nitrates resulted in significant reduction in right atrial pressure and pulmonary capillary wedge pressure. Hydralazine produced marked increase in cardiac index and decrease in systemic vascular resistance. The combined therapy produced decrease in both ventricular filling pressures along with an increase in cardiac index. Heart rate and arterial pressure were virtually unaffected. Statistically significant changes from control at the 0.01 and 0.001 levels are indicated by * and ** respectively (Chatterjee et al. 1978).

there was a significant reduction in systemic vascular resistance, associated with a marked increase in cardiac index and SV index. There was no or little change in pulmonary capillary wedge and right atrial pressures. When nitrates and hydralazine were combined right atrial and pulmonary capillary wedge pressures decreased significantly to levels comparable to those with nitrates alone. Furthermore there was a marked reduction in systemic vascular resistance. Cardiac index and SV indices rose to levels which were slightly higher than those with hydralazine alone. These findings suggest that the combined use of agents which selectively dilate the capacitance vessels and the arteriolar resistance vessels thereby producing a reduction in both preload and afterload can optimize the hemodynamic benefit of vasodilator therapy and potentially alleviate the symptoms of CHF

COMPARISON OF HEMODYNAMIC EFFECTS OF ORAL HYDRALAZINE AND PRAZOSIN

Oral hydralazine produces beneficial hemodynamic and clinical response in many patients with chronic CHF Undesirable side effects are not infrequently encountered particularly when a larger dose of hydralazine is needed There is, therefore a growing interest in identifying alternative vasodilators with similar or better potential for beneficial hemodynamic and clinical effects. In several recent investigations the hemodynamic effects of prazosin hydrochloride, a quinazoline antihypertensive agent have been investigated and it has been demonstrated that like hydralazine it improves *cardiac performance in patients with* chronic CHF However little information is available about the comparative hemodynamic effects of these two drugs in the same group of patients. Therefore the comparative hemodynamic effects of oral prazosin hydrochloride and hydralazine were evaluated in the same patients with chronic CHF (Chatterjee *et al* 1973) The initial dose of prazosin was 40 to 50 micrograms/kilogram (2 mg in four patients and 3 mg in seven patients), comparable with the dose selected by previous investigators Hemodynamic measurements were repeated *hourly Prazosin* was then given in doses increasing by one milligram at three hour intervals until a 5 mg dose was administered Nine patients received two additional 5 mg doses at eight hour intervals.

The initial oral dose of hydralazine was 50 mg, which was increased six hours later to 75 mg in ten of eleven patients. In one patient there was a large increase in CO with 50 mg of hydralazine and the dose was not increased Hemodynamic measurements were repeated hourly Oral hydralazine was then given at six hour intervals up to thirty six hours with frequent hemodynamic measurements. Hemodynamic measurements made at the time of maximum effect of th

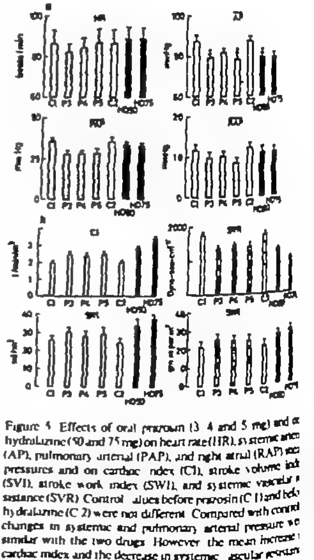

Figure 5 Effects of oral prazosin (3 4 and 5 mg) and oral hydralazine (50 and 75 mg) on heart rate (HR), systemic arterial (AP), pulmonary arterial (PAP), and right atrial (RAP) mean pressures and on cardiac index (CI), stroke volume index (SVI), stroke work index (SWI), and systemic vascular resistance (SVR) Control values before prazosin (C 1) and before hydralazine (C 2) were not different Compared with control changes in systemic and pulmonary arterial pressure were similar with the two drugs However the mean increase in cardiac index and the decrease in systemic vascular resistance with hydralazine were significantly greater than with prazosin. Hemodynamic changes after 3 4 or 5 mg prazosin were of similar magnitude P3 P4 and P5 = prazosin 3 4 and 5 mg HD50 HD75 = hydralazine 50 and 75 mg (Chatterjee *et al* 1979[b])

g on cardiac index were recorded at each dose level both drugs and compared.

The control hemodynamic data before the administration of prazosin or hydralazine, irrespective of the order of their administration, were remarkably similar. The hemodynamic effects of oral prazosin and hydralazine are illustrated in Figure 5. The hemodynamic changes after 3, 4 and 5 mg doses of oral prazosin were similar. Heart rate did not change significantly in any patient. There was a significant decrease in pulmonary artery wedge pressure, right atrial pressure and mean pulmonary and mean systemic arterial pressures. There was also a significant increase in cardiac index, along with a decrease in systemic vascular resistance. Stroke volume and stroke work indices increased in most patients, although the increase in stroke work index was not statistically significant. In the same patients maximal hemodynamic response, in terms of increase in CO was also observed at one to two hours after administration of oral hydralazine. There was a large increase in cardiac index (average 58 %) and a significant decrease in systemic vascular resistance. Stroke volume and stroke work indices increased greatly in most patients and a small decrease in pulmonary vascular resistance was also noted. There were only minimal changes in systemic and pulmonary venous pressures. Hemodynamic changes after 50 mg were less than those seen at 75 mg dose levels. During continued administration of 75 mg of hydralazine, hemodynamic changes were persistent.

Comparison of hemodynamic effects of hydralazine and prazosin in the same patients indicated that in the prescribed doses hydralazine produced greater hemodynamic effects than prazosin. The average increase in CO with hydralazine was 58 % compared with 25 % increase with prazosin, a highly significant difference ($p<0.001$). The decrease in calculated systemic vascular resistance during prazosin treatment (-20 %) was significantly less than that produced by hydralazine (-40 %) (Figure 6). The increase in stroke work and SV indices was also significantly greater with hydralazine than with prazosin. The decrease in systemic arterial mean pressure was small with both drugs. These findings indicate that though both drugs improved left ventricular performance, improvement with hydralazine was greater than with prazosin.

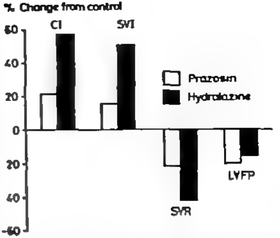

Figure 6. Comparison between the hemodynamic effects of prazosin (5 mg) and hydralazine (75 mg) in patients with chronic CHF. The magnitude of the decrease in left ventricular filling pressure (LVFP) was similar with both drugs. However the increase in cardiac index (CI) and stroke volume index (SVI) and the decrease in systemic vascular resistance (SVR) were greater with hydralazine than with prazosin. The differences between the changes in CI, SVI and SVR were statistically significant, whereas the difference between the changes in LVFP were not (Chatterjee *et al.* 1979[b]).

HYDRALAZINE IN VALVULAR REGURGITATION

In patients with mitral or aortic regurgitation the forward SV and effective CO are influenced not only by the severity (Braunwald *et al.* 1957; Greenberg *et al.* 1978; Wiggers & Feil 1922) of regurgitant lesion, but also by the degree of left ventricular outflow resistance. In patients with mitral regurgitation, for example, an elevated left ventricular outflow resistance enhances the regurgitant fraction and decreases the forward SV. With the reduction of left ventricular outflow resistance, left ventricular total SV is redistributed and there is an increase in forward SV associated with a reduction in regurgitant volume. It is not surprising, therefore, that vasodilator agents capable of reducing left ventricular outflow resistance should produce beneficial hemodynamic response in the presence of valvular regurgitation. Beneficial hemodynamic and clinical response to nitroprusside infusion in patients with mitral and aortic regurgitation have been documented (Chatterjee *et al.* 1973). Hydralazine, like nit

roprusside produces favorable changes in left ventricular dynamics in the presence of mitral or aortic regurgitation (Greenberg *et al* 1980) The hemodynamic effects of intravenous hydralazine (0 3 mg/kg) in ten patients with chronic severe mitral regurgitation are summarized in Table II Despite some decrease in mean arterial pressure heart rate did not change following hydralazine. Mean pulmonary arterial pressure decreased in most patients. In contrast to patients with chronic CHF in patients with mitral insufficiency a *decrease in mean pulmonary capillary wedge pressure* is consistently observed due to a reduction in the amplitude of the regurgitant "v" wave A decrease in the "v" wave suggests a reduction in the regurgitant volume Indeed when changes in regurgitant fraction were estimated from the difference between left ventricular total SV and forward SV it was apparent that during hydralazine therapy there was a significant reduction in regurgitant fraction Decreased regurgitant fraction was associated with an increase in forward SV although total SV of the left ventricle remained unchanged Thus hydralazine induced decreased systemic vascular resistance caused a redistribution of left ventricular total SV more blood now being pumped into the aorta and less to the left atrium (Figure 7). Left ventricular end-diastolic volume and ejection fraction however remained unchanged. The beneficial hemodynamic effects of intravenous hydralazine therapy were maintained following chronic oral hydralazine therapy (Figure 8) (next page)

Beneficial effects of hydralazine have also been reported in patients with aortic regurgitation (Greenberg *et al* 1980) An increase in forward CO and a reduction in pulmonary capillary wedge pressure have been observed in these patients during hydralazine therapy

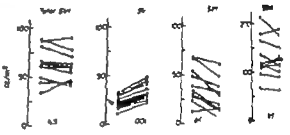

Figure 7 Changes in left ventricular volumes following intravenous hydralazine in a group of patients with severe mitral regurgitation Although total stroke volume index (Tot SVI) was not affected, forward stroke volume index (F-SVI) increased and regurgitant stroke volume index (R SVI) decreased. End-diastolic volume index (EDVI) did not change (Greenberg *et al* 1978)

Table II Hemodynamic effects of intravenous hydralazine in mitral regurgitation (Mean values ± SEM) (Chatterjee et al 1979*)

	Control	Hydralazine	p
Heart rate (beats/min)	90±7 (SEM)	90±5	NS
MAP (mm Hg)	99±5	87±5	<0 001
PAP (mm Hg)	47±6	41±5	<0 01
PCW (mm Hg)	33±4	25±3	<0 005
PCW "V" wave (mm Hg)	48±6	33±5	<0 005
LVEDP (mm Hg)	21±3	18±3	NS
Forward CI (L/min/m²)	2 0±0 1	3 0±0 2	<0 001
Forward SVI (ml/m²)	22±	33±3	<0 001
SVR (dyne-sec/cm⁵)	2100±170	1290±90	<0 001
EDVI (ml/m²)	130±14	120±12	NS
ESVI (ml/m²)	67±12	63±11	NS
Total SVI (ml/m²)	62±6	60±5	NS
Regurgitant SVI (ml/m²)	40±6	27±6	<0 001
Regurgitant fraction (%)	61±5	42±6	<0 001
Ejection fraction (%)	51±5	52±5	NS

MAP = mean arterial pressure; PAP = mean pulmonary artery pressure, PCW = mean pulmonary capillary wedge pressure; LVEDP = left ventricular end-diastolic pressure; CI = cardiac index SVI = stroke volume index SVR = systemic vascular resistance; EDVI = end-diastolic volume index, ESVI = end-systolic volume index (NS = not significant)

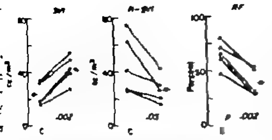

Figure 8 Effect of oral hydralazine on forward stroke volume index (F-SVI), regurgitant stroke volume index (R-SVI), and regurgitant fraction (RF) in five patients with chronic mitral regurgitation. With hydralazine F-SVI increased as R-SVI and RF decreased (Greenberg *et al* 1978)

Although beneficial hemodynamic effects of hydralazine in patients with mitral or aortic regurgitation have been demonstrated its role in the clinical management of such patients has not been clearly defined Undoubtedly the surgical correction of the valvular lesion is the definitive treatment for these patients However there are some clinical situations in which surgery is contraindicated or needs to be deferred. Patients with mitral regurgitation complicating acute myocardial infarction, those with chronic mitral regurgitation and poor left ventricular function, or those with associated medical problems might temporarily or chronically benefit from long term hydralazine therapy

EFFECTS OF HYDRALAZINE THERAPY ON REGIONAL HEMODYNAMICS

Although there is ample evidence that hydralazine therapy improves overall cardiac performance in patients with chronic CHF information regarding its effect on regional circulation and hemodynamics are scanty The vasodilatory effects of hydralazine are neither uniform, nor of equal magnitude, on all peripheral vascular beds. The resistance vessels of the coronary renal, splanchnic and cerebral vascular beds are affected more than those in the skin and skeletal muscles. It is, therefore, imperative to evaluate the effects of hydralazine therapy on regional circulation and function, in addition to its effects on cardiac dynamics

The vasodilatory effects of hydralazine on the renal vascular bed has important clinical significance, particularly in patients with chronic CHF In patients with chronic heart failure, renal vascular resistance along with total systemic vascular resistance decreases. Renal blood flow in association with CO also tends to increase (Cogan *et al* 1980). Glomerular filtration rate remains unchanged but filtration fraction falls Excretion of sodium plus potassium is also enhanced in these patients following hydralazine therapy

Hydralazine induced changes in coronary hemodynamics are of particular significance, especially when it is used for the management of patients with CHF due to ischemic heart disease. Changes in coronary hemodynamics, myocardial oxygen consumption and myocardial lactate extraction, along with changes in left ventricular performance following the administration of 100 mg of oral hydralazine in a group of patients with chronic ischemic CHF are summarized in Table III As expected there was a significant increase in CO and a decrease in systemic vascular resistance there was a tendency to a lower left ventricular filling pressure There was no significant

Table III Changes in coronary hemodynamics following oral hydralazine in chronic ischemic CHF

	Control	Hydralazine	p
HR x PSP (mm Hg/min 10^{-3})	10.6±2.5	10.6±2.3	NS
SVR (dynes sec-cm^{-5})	1395±311	990±166	0.01
PCWP (mm Hg)	16.5±7.8	14.0±6.2	NS
CI (ml/min)	2.2±0.45	2.9±0.45	0.01
CSF (ml/min)	46±41	60±51	NS
MVO_2 (ml/min) 10^{-}	8.2±5.5	8.6±6.9	NS
Art CSO_2 (ml/100 ml)	12.3±1.1	12.1±1.3	NS
% Lactate	38±14	41±20	NS

HR PSP = Product of heart rate and peak systolic arterial pressure SVR = systemic vascular resistance; PCWP = pulmonary capillary wedge pressure, CI = cardiac index, CSF = coronary sinus flow MVO_2 = myocardial oxygen consumption. Art CSO_2 = myocardial oxygen extraction, % = myocardial lactate extraction (NS = not significant)

change in the product of the peak systolic pressure and the heart rate – an index of myocardial oxygen demand Consequently there was no change in coronary sinus flow an approximation of coronary blood flow As arterial-coronary sinus oxygen content difference did not change there was no change in calculated myocardial oxygen consumption Transmyocardial lactate extraction also remained unchanged in the majority of patients and in the group as a whole transmyocardial lactate extraction before hydralazine therapy was +38 % and + 41 % following hydralazine therapy In most patients there was a significant increase in CO with little or no change in left ventricular filling pressure indicating enhanced cardiac performance. A lack of a concomitant increase in myocardial oxygen consumption suggests that the improved mechanical function in these patients occurred without an increase in the metabolic cost

EFFECTS OF HYDRALAZINE THERAPY ON CARDIAC PERFORMANCE DURING EXERCISE

Although several studies have confirmed that hydralazine therapy can produce improvement in resting left ventricular performance in patients with chronic CHF only limited data are available about changes in cardiac reserve during exercise with hydralazine therapy (Michael *et al* 1979 Rubin *et al* 1979). Many patients with chronic CHF do not have symptoms of diminished cardiac reserve at rest and such symptoms only become manifest during exercise. It is therefore desirable to evaluate the changes in cardiac reserve in these patients during exercise. Changes in exercise hemodynamics in patients with chronic CHF during supine bicycle exercise before and after short term oral hydralazine therapy are summarized in Table IV Following addition of hydralazine to conventional therapy there was a significant increase in resting CO and SV There was no significant change in pulmonary capillary wedge pressure. Increased CO and SV with no change in pulmonary capillary wedge pressure indicated improvement in left ventricular function at rest. During exercise following hydralazine therapy CO and SV remained elevated The magnitude of exercise-induced increase in heart rate was similar to that during conventional therapy Pulmonary capillary wedge pressure also increased by similar magnitude. Resting systemic vascular resistance decreased significantly but there was no further decrease during exercise. Elevated CO at rest and during exercise at similar levels of left ventricular filling pressures following hydralazine compared to those during conventional therapy indicated an upward and parallel shift of left ventricular function curve. These findings suggest improved cardiac performance during exercise-induced stress.

Despite a significant improvement in cardiac performance during exercise in these patients, their work capacity and the total body oxygen consumption remained unchanged following short term hydralazine therapy (Figure 9). Before the addition of hydralazine CO was lower but the oxygen extraction was greater Following addition of hydralazine CO increased but the oxygen extraction during exercise decreased proportionately therefore oxygen consumption remained

Table IV Effects of oral hydralazine on hemodynamics at rest and during exercise (Chatterjee *et al* 1979[a])

Therapy	CO (L/min)	PA SAT (%)	SV (ml)	HR (beats/min)	LVFP (mm Hg)	AP (mm Hg)	PA (mm Hg)	RA (mm Hg)	W KPM
C R	3 2±8	58±10	37±10	88±23	23±8	87±11	35±9	11±8	
C E	4.6±1.5	35±7	40±11	113±30	33±7	102±11	48±10	18±11	180±121
H R	4.8±1.2	70±7	49±15	93±22	23±8	84±10	33±10	11±10	
H E	5.9±1.8	47±8	48±15	119±31	33±6	95±13	50±9	19±12	100±127
p of R R	<0 01	<0 01	<0 01	NS	NS	NS	NS	NS	
p of E E	<0 01	<0 01	<0 01	<0 01	NS	<0 05	NS	NS	

C = conventional therapy H = hydralazine; R = rest E = exercise CO = cardiac output PA SAT = mixed oxygen saturation, SV = stroke volume; HR = heart rate; LVFP = left ventricular filling pressure; AP = mean arterial pressure PA = mean pulmonary artery pressure; RA = mean right atrial pressure, W = peak exercise workload (NS = not significant

Lack of increase in oxygen consumption rcise has also been observed with the use sodilator agents (Rubin *et al* 1979ᵃ). It is by improvement in oxygen consumption capacity during exercise did not occur in nts, despite an increase in CO and despite potential for increased oxygen extraction changes in work capacity and peak oxygen on during exercise may be different follow rm hydralazine therapy compared to those term hydralazine therapy Preliminary data hat, at least in some patients, oxygen con and maximum work capacity improve fol g term therapy with hydralazine (Figure 10)

IODYNAMIC EFFECTS OF LONG ERM HYDRALAZINE THERAPY IN CHRONIC CHF

to assess the clinical efficacy of chronic va therapy for CHF and before such therapy can be recommended for the long term management of patients w th chronic CHF it is desirable to know if the hemodynamic effects of vasodilator agents are maintained during chronic therapy Little information is available on the persistence of hemodynamic effects during maintenance therapy with hydralazine in patients with chronic refractory CHF Therefore the hemodynamic effects of oral hydralazine were deter mined in a group of patients with chronic CHF not only at the start of therapy but also after its long term use (Chatterjee *et al* 1979ᵇ Chatterjee *et al* 1980) Hemodynamic effects were also evaluated following withdrawal of hydralazine after chronic ther apy There were eleven patients with chronic CHF refractory to conventional therapy At the time of initial hemodynamic study seven of eleven patients were in the New York Heart Association Class IV and four patients in Class III. Clinically all patients had signs of biventricular failure, pulmonary arterial hypertension and cardiomegaly In one patient 50 mg, and n another 100 mg, of oral hydralazine were administered every six hours In the remaining nine patients, 75 mg. four times daily produced the best hemodynamic response All patients then continued

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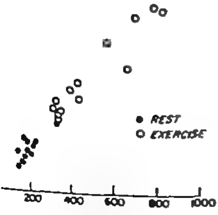

) Effect of short-term hydralazine therapy on oxygen ption in group of patients with chronic CHF com conventional therapy there was no significant change in consumption at rest or during peak exercise (Chat t al 1979ᵃ).

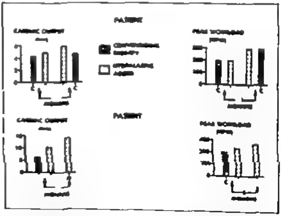

Figure 10 Comparison of acute and chronic exercise hemodynamics in two patients with chronic CHF who received maintenance hydralazine therapy (Top Patient 3): CO and peak exercise work load increased after long term (11 months) therapy although following initiation of therapy peak work load did not change despite some increase in CO In Patient 9 (bottom), following six months of therapy peak work load increased significantly

change in the product of the peak systolic pressure and the heart rate – an index of myocardial oxygen demand Consequently there was no change in coronary sinus flow an approximation of coronary blood flow As arterial-coronary sinus oxygen content difference did not change there was no change in calculated myocardial oxygen consumption Transmyocardial lactate extraction also remained unchanged in the majority of patients and in the group as a whole transmyocardial lactate extraction before hydralazine therapy was +38 % and + 41 % following hydralazine therapy In most patients there was a significant increase in CO with little or no change in left ventricular filling pressure indicating enhanced cardiac performance. A lack of a concomitant increase in myocardial oxygen consumption suggests that the improved mechanical function in these patients occurred without an increase in the metabolic cost

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Despite a significant improvement in cardiac performance during exercise in these patients, their work capacity and the total body oxygen consumption remained unchanged following short term hydralazine therapy (Figure 9). Before the addition of hydralazine CO was lower but the oxygen extraction was greater Following addition of hydralazine CO increased, but the oxygen extraction during exercise decreased proportionately therefore oxygen consumption remained

Table IV Effects of oral hydralazine on hemodynamics at rest and during exercise (Chatterjee *et al* 1979).

Therapy	CO (L/min)	PA SAT (%)	SV (ml)	HR (beats/min)	LVFP (mm Hg)	AP (mm Hg)	PA (mm Hg)	RA (mm Hg)	W KPM
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H E	5 9±1 8	47±8	48±15	119±31	33±6	95±13	50±9	19±12	100±127
p of R R	<0 01	<0 01	<0 01	NS	NS	NS	NS	NS	
p of E E	<0 01	<0.01	<0 01	<0.01	NS	<0.05	NS	NS	

C = conventional therapy H = hydralazine; R = rest, E = exercise; CO = cardiac output, PA SAT = mixed oxygen saturation; SV = stroke volume; HR = heart rate; LVFP = left ventricular filling pressure, AP = mean arterial pressure; PA = mean pulmonary artery pressure; RA = mean right atrial pressure; W = peak exercise workload (NS = not significant)

unchanged. Lack of increase in oxygen consumption during exercise has also been observed with the use of other vasodilator agents (Rubin *et al.* 1979a). It is not clear why improvement in oxygen consumption and work capacity during exercise did not occur in these patients, despite an increase in CO and despite having the potential for increased oxygen extraction. However, changes in work capacity and peak oxygen consumption during exercise may be different following long term hydralazine therapy compared to those after short term hydralazine therapy. Preliminary data indicate that, at least in some patients, oxygen consumption and maximum work capacity improve following long term therapy with hydralazine (Figure 10).

HEMODYNAMIC EFFECTS OF LONG TERM HYDRALAZINE THERAPY IN CHRONIC CHF

In order to assess the clinical efficacy of chronic vasodilator therapy for CHF and before such therapy can be recommended for the long term management of patients with chronic CHF, it is desirable to know if the hemodynamic effects of vasodilator agents are maintained during chronic therapy. Little information is available on the persistence of hemodynamic effects during maintenance therapy with hydralazine in patients with chronic refractory CHF. Therefore, the hemodynamic effects of oral hydralazine were determined in a group of patients with chronic CHF not only at the start of therapy but also after its long term use (Chatterjee *et al.* 1979b; Chatterjee *et al.* 1980). Hemodynamic effects were also evaluated following withdrawal of hydralazine after chronic therapy. There were eleven patients with chronic CHF refractory to conventional therapy. At the time of initial hemodynamic study, seven of eleven patients were in the New York Heart Association Class IV and four patients in Class III. Clinically, all patients had signs of biventricular failure, pulmonary arterial hypertension and cardiomegaly. In one patient 50 mg, and in another 100 mg, of oral hydralazine were administered every six hours. In the remaining nine patients, 75 mg, four times daily, produced the best hemodynamic response. All patients then continued

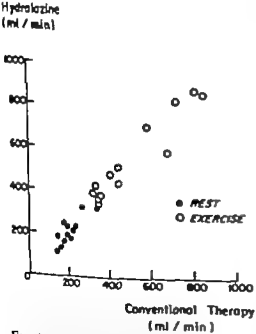

Figure 9. Effect of short-term hydralazine therapy on oxygen consumption in a group of patients with chronic CHF compared to conventional therapy: there was no significant change in oxygen consumption at rest or during peak exercise (Chatterjee *et al.* 1979a).

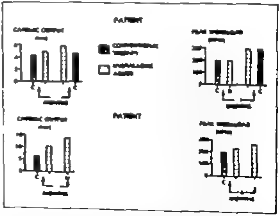

Figure 10. Comparison of acute and chronic exercise hemodynamics in two patients with chronic CHF who received maintenance hydralazine therapy (Top: Patient 3): CO and peak exercise work load increased after long term (11 months) therapy, although following initiation of therapy peak work load did not change despite acute increase in CO. Patient 9 (bottom), following six months of therapy, peak work load increased significantly.

the same dose during maintenance therapy

Hemodynamic measurements were repeated three to sixteen months (average 8.3 months) after continued hydralazine therapy Five patients were restudied between three and six months and four between seven and nine months after maintenance therapy The remaining two patients were restudied at 14 and 16 months respectively In seven of eleven patients hemodynamic measurements were repeated after withdrawal of hydralazine therapy The hemodynamic effects of oral hydralazine at the beginning of therapy and after maintenance therapy and following withdrawal of hydralazine are summarized in Table V No significant change in heart rate or mean arterial or mean pulmonary artery pressure occurred either at the beginning or during maintenance therapy After discontinuation of hydralazine therapy there was also no significant change in heart rate arterial pressure or pulmonary artery pressure. Calculated systemic vascular resistance decreased significantly (-40 %) aft the start of therapy and remained lower (-41 %) durin maintenance therapy Along with the decreased sys temic vascular resistance, CO SV and stroke vol indices increased. Left ventricular stroke work inde at the beginning of therapy increased by 68 % an remained elevated during maintenance thera (+97 %). Changes in cardiac index and stroke volum index in individual patients after initiation and durin maintenance therapy and after withdrawal of hydra azine are shown in Figure 11 (next page). In ten o eleven patients cardiac index increased initially an remained elevated during maintenance therapy Sim larly stroke volume index increased initially and r mained elevated during maintenance therapy Hydra azine induced increase in stroke volume index durin maintenance therapy was 88 % and it was greater th that at the beginning of therapy (+59 %). Sustain increase in CO or SV with little or no change in le

Table V The hemodynamic effects of oral hydralazine at the beginning of therapy and after maintenance therapy a following withdrawal of hydralazine (Mean ± SEM).

	Heart rate (beats/mm)	Mean arterial pressure (mm Hg)	Mean pulmonery artery pressure (mm Hg)	Mean pulmonary capillary wedge pres (mm Hg)	Mean right atrial pressure (mm Hg)
Control (N = 11)	91 1±22.9*	88.1±12 7	38 7±13 7	24.3±11 7	12.1±8 2
Initial hydralazine therapy (N = 11)	88.18±15 3	83 6±8.7	36 7±12 1	20.5±8 6	11.3±8 2
Late hydralazine therapy (N = 11)	79 8±12 4	[illegible]8±11 3	31 5±9 8	[illegible]8±5.8	10 1±4 7
Off hydralazine therapy (N = 7)	74 8±11 4	82 8±10 3	31 2±7 6	21 0±6 2	8 6±4 3
Statistical significance					
Control versus initial hydralazine therapy	NS	NS	NS	NS	NS
Control versus late hydralazine therapy	NS	NS	0 05	NS	NS
Initial hydralazine therapy versus late hydralazine therapy	NS	NS	NS	NS	NS
Late hydralazine therapy versus off hydralazine therapy	NS	NS	NS	NS	NS
Control versus off hydralazine therapy	NS	NS	NS	NS	NS

Mean ± SD (NS = not significant)

ventricular filling pressure indicated persistent improvement in cardiac performance during maintenance hydralazine therapy in these patients.

The results of this investigation suggest that the hemodynamic effects of oral hydralazine persist during its continued use. The magnitude of increase in CO, SV and stroke work during the late hemodynamic study was similar to that observed after initiation of oral hydralazine therapy. Similarly, the magnitude of reduction in systemic vascular resistance at the beginning of and during maintenance therapy was also similar. That hydralazine therapy has the potential to maintain a sustained improvement in cardiac performance during long term therapy is also evident from the fact that after withdrawal of hydralazine therapy the hemodynamic changes declined gradually and returned almost to the control values. Concomitant with the decrease in CO, systemic vascular resistance increased while left ventricular filling pressure remained unchanged. This deterioration in hemodynamic findings and cardiac performance after withdrawal of hydralazine occurred despite continual bed rest and continuation of conventional therapy. It needs to be emphasized, however, that the observation period in this particular study was relatively short and the number of patients studied was small. Further studies will be needed to evaluate how long these beneficial hemodynamic effects of hydralazine persist in patients with chronic CHF and what is the impact of such therapy on the prognosis of such patients.

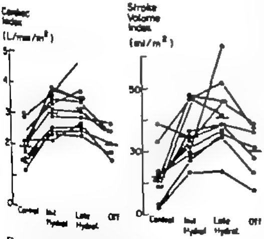

Figure 11. Changes in cardiac and stroke volume indices in individual patients at the beginning (initial hydralazine) and during maintenance hydralazine therapy (late hydralazine), and after withdrawal of hydralazine (off). Cardiac index and stroke volume index increased initially and remained elevated during maintenance therapy. After withdrawal of hydralazine, cardiac and stroke volume indices decreased towards the control (Chatterjee *et al.* 1980).

INFLUENCE OF HYDRALAZINE THERAPY ON PROGNOSIS OF PATIENTS WITH CHRONIC REFRACTORY CHF

Admittedly, without a matched control and prospective study, the impact of vasodilator therapy on the prognosis of patients with severe chronic refractory CHF cannot be assessed. However, adequate, although not precise, knowledge is available regarding the prognosis of such patients with conventional therapy from many retrospective studies (Hamby 1970, Kaushik *et al.* 1975, Nelson *et al.* 1975, Vlietstra *et al.* 1977). It is, therefore, possible to gain some insight about the potential impact of vasodilator therapy on the prognosis of such patients when the results of vasodilator therapy are compared to those previously reported results with conventional therapy. In order to assess the clinical efficacy of chronic vasodilator therapy the long term results were evaluated in 56 patients treated with hydralazine, usually in combination with nitrates during a follow-up period of thirteen months (mean) (range three to thirty months) (Massie *et al.* 1980). Thirty-seven of 56 patients were males and 19 were females. Etiology of CHF was ischemic heart disease (IHD) in 34, primary myocardial disease in 9, hypertension in 7, rheumatic heart disease in 4, and uncertain in 2. The mean duration of CHF was 3.5 years (range: four months to 17 years). In thirty patients symptoms of CHF were gradually worsening prior to starting vasodilators while they were considered stable in 26. When vasodilator therapy was instituted 45 were considered New York Heart Association Class IV and 11 were Class III. The maintenance doses of hydralazine were 200 to 400 mg daily, and of nitrates 5 to 20 mg sublingual isosorbide dinitrate every two to three hours or 40 to 80 mg oral isosorbide dinitrate every four to six hours.

Overall survival, plotted by the life table method,

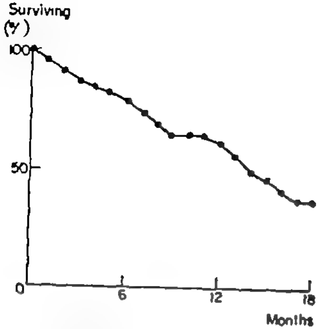

Figure 12. Cumulative survival of 56 patients with severe CHF after initiation of hydralazine/nitrate therapy. This patients population includes those who discontinued vasodilator therapy during the follow up period. In the group as a whole, 6, 12 and 18 months survival rate were 78, 63 and 37 %, respectively (Massie *et al.* 1980)

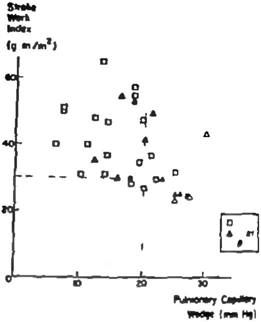

Figure 13. Clinical outcome of patients as a function of initial hemodynamics. □ indicates improved patients; Δ no improvement. Solid symbols (▲ ■) indicate those patients who died and open symbols (Δ □) indicates those who are alive. Patient with pulmonary capillary wedge (PCW) below 30 mm Hg generally improved, while those with PCW > 30 mm Hg usually did not. Patients with SWI < 30 g-m/m² usually did not survive. The combination of these measurements were particularly predictive of clinical response (Massie *et al.* 1980)

is illustrated in Figure 12. Two patients, who died of causes unrelated to cardiac disease, are excluded. Six, twelve and eighteen months (the last point at which an adequate number of patients remained under follow up) survival rates were 78 %, 63 % and 37 % respectively. The cause of death was sudden death in ten, progressive CHF in eight, myocardial infarction (MI) in five, nonspecified cardiac death in four and carcinoma in two. Thus, the mortality rate of this group of patients remained substantial (22 % at six months and 38 % at twelve months). Again, without a comparable control group, it is difficult to speculate whether vasodilators resulted in a change of prognosis. Several previous investigations, however, have reported a very high mortality rate in the comparable group of patients. Nelson reported a 50 % mortality at a mean follow up of fourteen months in patients with severe CHF associated with low ejection fraction and abnormal hemodynamics (Nelson *et al.* 1975). Another study noted a 55 % one year mortality in patients with ischemic CHF with ejection fraction below 25 %, who probably would have been comparable to the patients in this study (Vlietstra *et al.* 1977). In a series of patients with primary cardiomyopathy, Hamby noted a 54 % mortality at a mean follow up of fifteen months in those with significant hemodynamic abnormalities (Hamby 1970). A preliminary report described a 46 % one year mortality in 39 patients with chronic CHF maintained on isosorbide dinitrate, in addition to conventional therapy (Kaushik *et al.* 1975). Thus the survival in the present study appears to be somewhat better than those previously reported. In the present study an attempt was made to evaluate the potential predictors for better prognosis with vasodilator therapy. Of the clinical factors, only pretreatment New York Heart Association Class III (rather than Class IV), and lack of progressive CHF indicated a better response. The severity of depression of cardiac function based on hemodynamic indices before the initiation of vasodilator therapy was also related to the long term prognosis (Figure 13). Thus, the patients with a pulmonary capillary wedge pressure of 30 mm Hg

or more had a significantly higher mortality compared to those with a lower initial pulmonary capillary wedge pressure. Similarly patients with an initial stroke work index of 30 g-m/m² or less had a worse mortality. The combination of these two measurements was highly correlated with subsequent outcome. Thus, the survival rate in patients with stroke work index more than 30 g-m/m² and pulmonary capillary wedge pressure below 30 mm Hg was 69 % compared to only 31 % in patients with both stroke work index less than 30 g-m/m² and pulmonary capillary wedge pressure exceeding 30 mm Hg.

The magnitude of hemodynamic improvement and improvement in cardiac function during the initiation of vasodilator therapy was also helpful to assess the long term prognosis in patients with chronic CHF. A plot of stroke work index versus pulmonary capillary wedge pressure after initiation of vasodilator therapy (Figure 14) indicates how these measurements predicted long term prognosis. Thus, 15 of 20 patients (75 %) who had stroke work index of more than 30 g-m/m² and pulmonary capillary wedge pressure less than 20 mm Hg following initiation of hydralazine therapy survived. This can be opposed to 5 of 34 patients (14 %) with either stroke work index less than 30 g-m/m² or pulmonary capillary wedge pressure more than 20 mm Hg which survived at the time of the latest follow-up. Patients who discontinued vasodilator therapy or had progressive symptomatology despite initial hemodynamic improvement also had a poorer prognosis in terms of survival.

It needs to be emphasized that although this retrospective study suggests a better prognosis with hydralazine/nitrate therapy in certain subsets of patients with severe refractory CHF, further long term studies utilizing objective methods of evaluation will be necessary to assess the impact of vasodilator therapy on the prognosis of patients with chronic CHF. Nonetheless, our findings indicate that the vasodilator therapy with a combination of hydralazine and nonparenteral nitrates provides symptomatic relief in many patients with severe chronic CHF. Symptomatic improvement may persist in many patients for several months. There is also evidence that some clinical predictors can be utilized to assess long term prognosis in these patients. It also seems that the hemodynamic

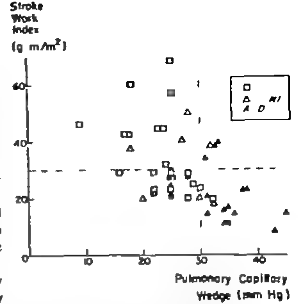

Figure 14. Hemodynamic measurements are plotted following the acute administration of vasodilator agents, as correlated with subsequent clinical response. The same general findings hold for this data as shown in Figure 13. The dashed line (----) for wedge pressure has been shifted to 20 mm Hg to generally separate those patients in the lower right hand quadrant who did poorly from those patients in the upper left hand quadrant who did well (Massie *et al.* 1980).

evaluation before and after initiation of treatment may be useful not only to assess the response to vasodilators, but also to assess in part the expected prognosis in these patients.

ADVERSE REACTIONS TO VASODILATOR THERAPY

Side effects and drug toxicity at the initiation and during maintenance hydralazine therapy were not uncommon (Table VI)(next page). Gastrointestinal symptoms (nausea, vomiting, anorexia) and headaches were the most common problem, although they frequently improved with time. Several more serious adverse reactions occurred, including drug induced lupus erythematosis, peripheral neuropathy, symptomatic hypotension and worsening angina pectoris. These complications led to the discontinuation of therapy in six

Table VI Adverse reactions to vasodilator therapy (N = 56 patients)

Adverse reaction	Number of patients	Number stopping therapy
Nausea vomiting	16	5
Headache	8	2
Drug induced SLE	3	2
Hypotension	3	2
Diarrhea	2	1
Peripheral neuropathy	1	1
Fluid retention	2	0
Worsening angina	1	1
Any	24	10*

Note some patients experienced more than one adverse reaction, and therapy was sometimes discontinued for a combination of reasons.

patients Acetylation rate was measured in fifteen patients with adverse reactions. All patients with lupus erythematosus were slow acetylators but other forms of toxicity did not appear to be related to acetylation phenotype.

SUMMARY

In summary these investigations indicate that oral hydralazine produces beneficial hemodynamic effects in patients with chronic CHF These favorable hemodynamic responses are observed in the presence or absence of mechanical defects, such as mitral or aortic regurgitation The predominant hemodynamic effects of hydralazine are substantial increase in CO and SV with decreased systemic vascular resistance. These investigations further suggest that hydralazine therapy not only improves resting cardiac performance, but also cardiac performance during exercise. There is also evidence that improved cardiac performance is sustained at least in some patients during maintenance hydralazine therapy The impact of hydralazine therapy on the long term prognosis of patients with refractory CHF however remains unknown Nevertheless the preliminary retrospective studies suggest that in certain subsets of patients with severe chronic CHF such therapy may provide a better prognosis compared to that expected with conventional therapy

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Table VI Adverse reactions to vasodilator therapy (N = 56 patients).

Adverse reaction	Number of patients	Number stopping therapy
Nausea, vomiting	16	5
Headache	8	2
Drug induced SLE	3	2
Hypotension	3	2
Diarrhea	2	1
Peripheral neuropathy	1	1
Fluid retention	2	0
Worsening angina	1	1
Any	24	10*

Note some patients experienced more than one adverse reaction and therapy was sometimes discontinued for a combination of reasons.

patients. Acetylation rate was measured in fifteen patients with adverse reactions. All patients with lupus erythematosus were slow acetylators but other forms of toxicity did not appear to be related to acetylation phenotype.

SUMMARY

In summary these investigations indicate that oral hydralazine produces beneficial hemodynamic effects in patients with chronic CHF These favorable hemodynamic responses are observed in the presence or absence of mechanical defects, such as mitral or aortic regurgitation The predominant hemodynamic effects of hydralazine are substantial increase in CO and SV with decreased systemic vascular resistance. These investigations further suggest that hydralazine therapy not only improves resting cardiac performance, but also cardiac performance during exercise There is also evidence that improved cardiac performance is sustained at least in some patients during maintenance hydralazine therapy The impact of hydralazine therapy on the long term prognosis of patients with refractory CHF however remains unknown Nevertheless, the preliminary retrospective studies suggest that in certain subsets of patients with severe chronic CHF such therapy may provide a better prognosis compared to that expected with conventional therapy

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MANAGEMENT OF REFRACTORY CHF WITH PRAZOSIN IMPORTANCE OF TOLERANCE AND TACHYPHYLAXIS

Nayab A Awan Mark K Evenson Kathleen E Needham and Dean T Mason*

ACUTE HEMODYNAMIC AND SYSTEMIC CIRCULATORY EFFECTS OF PRAZOSIN

Cardiac function was assessed by a Swan-Ganz thermodilution catheter positioned in the pulmonary artery Thereby pulmonary artery pressures were measured directly and cardiac output (CO) was determined using iced saline solution Systemic arterial pressures were directly recorded via a Teflon catheter introduced into the left brachial or radial artery

Following the acquisition of control cardiac and peripheral circulatory hemodynamic measurements, 46 µg/kg of oral prazosin was ingested and cardiocirculatory hemodynamic variables were repeated every 30 minutes for 6 hours in all patients (Awan *et al* 1977). Heart rate was 80±5 beats/min during control and remained unchanged during the 6 hours of measurement following the administration of prazosin Systemic arterial BP declined ($p<0.001$) throughout the period after prazosin ingestion (Figure 1A) Oral prazosin resulted in dramatic and sustained decrease ($p<0.001$) in the markedly increased control left ventricular filling pressure (LVFP) of 32 0±3 7 mm Hg (Figure 1B) Simultaneously with the reduction of LVFP oral prazosin caused a striking and persistent increase ($p<0.001$) in the control cardiac index of 1 95±0 12 l/min/m^2 (Figure 1C) At the same time, stroke work index (Figure 2B) (next page) increased ($p<0.01$) from control of 24 1±4 6 throughout the observation period This enhancement in cardiac performance was accomplished with less myocardial oxygen consumption estimated as pressure-time/minute which declined from a control of 3 175±139 mm Hg-sec/min to 2,931±242 ($p<0.01$) at 30 minutes, 2,554±170 ($p<0.001$) at 60 minutes with the improvement in mechanical efficiency lasting for the duration of study

Total systemic vascular resistance of 2,314±107 dynes-sec-cm^{-5} was lowered by oral prazosin throughout the duration of the study (Figure 2C) Prazosin

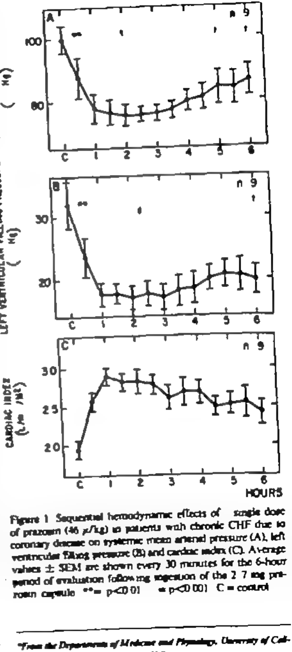


Figure 1 Sequential hemodynamic effects of single dose of prazosin (46 µ/kg) in patients with chronic CHF due to coronary disease on systemic mean arterial pressure (A), left ventricular filling pressure (B) and cardiac index (C). Average values ± SEM are shown every 30 minutes for the 6-hour period of evaluation following ingestion of the 2 7 mg prazosin capsule **= p<0 01 * = p<0 001 C = control

*From the Departments of Medicine and Physiology, University of California, San Francisco, California, U S A

[...]eased from 5.7±0.4 to 5.4 to 0.4 cm (p<0.001) (Figure 3A and 4) with prazosin therapy whereas LVESD diminished from 4.3±0.4 to 3.9±0.4 cm (p<0.001) (Figures 3B and 4). In addition, the long-term administration of oral prazosin resulted in an increase in shortening fraction from 27.6±6.4 to 30.2±4.5 percent (p<0.005) (Figure 3C), whereas mean normalized velocity of circumferential fiber shortening increased from 0.85±0.17 to 0.94±0.19 circumferences/sec (p<0.025) (Figure 3D).

LONG-TERM EFFECTS OF PRAZOSIN ON EXERCISE TOLERANCE

Following echocardiographic estimation of ventricular function, each of the patients underwent determination of maximal exercise capacity using graduated multistage treadmill exercise tests, before and during prazosin therapy (2 to 7 mg orally four times daily) (Awan et al. 1977b). Resting blood pressure prior to exercise was significantly reduced by prazosin. Systolic blood pressure (SBP) decreased from 132.6±8.9 to 112.6±6.7 mm Hg (p<0.001), whereas diastolic blood pressure decreased from 83.5±3.6 to 75.2±2.6 mm Hg (p<0.001). Resting mean BP was reduced from 100.4±5.4 to 88.3±6.1 mm Hg (p<0.0001). Resting heart rate was unchanged by prazosin; control 80±4 to 77±4 beats/min. Orthostatic hypotension was not observed in any patient treated with prazosin; control standing SBP declined 5.0±1.5 mm Hg and only 7.2±2.0 mm Hg with prazosin.

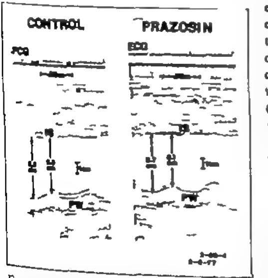


Figure 4. Representative example of the actions of long-term oral prazosin therapy on left ventricular dimensions in a single coronary disease patient with chronic severe CHF. The left panel, obtained prior to the initiation of oral prazosin therapy, shows an end-diastolic dimension (EDD) of 5.9 cm and an end systolic dimension (ESD) of 5.3 cm. The right panel, recorded two weeks following initiation of oral prazosin therapy (4 mg four times daily), demonstrates a decline of EDD to 5.7 cm, whereas ESD diminished to 5.1 cm. IS = interventricular septum; PW = left ventricular posterior wall.

Exercise capacity was assessed prior to prazosin therapy and two weeks after continuous treatment with the vasodilator agent. The aforementioned hemodynamic and echographic improvements in cardiocirculatory variables induced by prazosin resulted in enhanced exercise capacity (Awan et al. 1977b). All patients were able to exercise for a longer period, the mean duration of exercise improving from 209±39 to 317±50 seconds (p<0.001). In addition, maximal oxygen consumption increased from 10.2±1.4 to 13.7±1.7 ml/kg/min (p<0.01). This improvement in exercise tolerance was accomplished at less cardiac oxygen requirements as reflected by the reduction of the double product of HR and SBP, the indirect index of MVO_2. Control double product was significantly decreased at peak exercise during long-term prazosin therapy from 20,536±1,459 to 17,538±1,088 units (p<0.001). Since maximal exercise heart rate was not significantly altered (control 122±7 and prazosin 128±8 beats/min), the reduction in HR SBP product was accomplished by a decline in peak exercise SBP from 165.0±8.7 to 137.3±3.9 mm Hg (p<0.001).

LONG-TERM EFFECTS OF PRAZOSIN ON SYMPTOMS

The mean duration of follow-up of prazosin therapy exceeded 12 months (Awan et al. 1977b). Symptoms due to CHF were greatly diminished with prazosin in all nine patients (Figure 5). Prior to initiation of prazosin therapy, despite therapy with digoxin and diuretics, all patients had marked dyspnea and fatigue. Figure 5 shows considerable decrease in the symptoms of CHF achieved with 3 months long-term oral prazosin therapy in our patients. Extended (>12 months) follow-up of our patients indicated persistence of symptomatic benefit, the functional class being main-

increased forearm blood flow from 1.29±0 14 to 1 71±0 25 ml/100 g/min ($p<0.05$ versus control) at 60 minutes. Forearm blood flow remained increased for the entire 6 hours Forearm vascular resistance was lowered by prazosin in all patients at 30 minutes from 88 9±13 8 to 58 4±6 1 mm Hg/ml/100 g/min ($p<0.01$) and was further reduced to 47 9±5 8 (−47 per cent) ($p<0.001$ versus control) 1 hour after the administration of prazosin. The decline persisted for the 6-hour study period

Venous tone in the forearm was also lowered by prazosin from 58 9±13 8 to 18.5±3 9 ml/mm Hg (−69 per cent) ($p<0.001$ versus control) by 30 minutes and remained at this level for the entire 6-hour observation period The ratio of per cent reduction of forearm vascular resistance to per cent decline in forearm venous tone was 0 67 at 1 hour after prazosin administration, thereby indicating that the drug produced relatively more, although not statistically different ($p>0.05$), venous than arteriolar dilation. In addition, this relation was essentially unchanged throughout the 6-hour study period, indicating that the relative arteriolar and venodilator actions of prazosin remained constant.

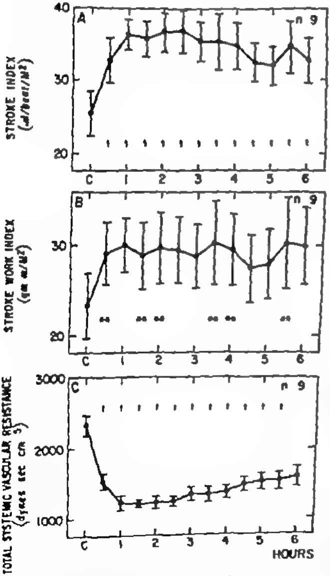


Figure 2. Serial cardiocirculatory actions of oral prazosin on stroke index (A), stroke work index (3) and total systemic vascular resistance (C) Format and patients same as in Figure 1 = $p<0.05$

LONG TERM EFFECTS OF PRAZOSIN ON VENTRICULAR FUNCTION EVALUATED BY ECHOGRAPHY

Ventricular function was assessed echocardiographically before and after two weeks of continuous therapy with 2 to 7 mg prazosin orally four times a day in all 9 patients.

In all patients prazosin resulted in a decline in left ventricular (LV) dimensions at both end-diastole (EDD) and end systole (ESD). Thus, LVEDD de-

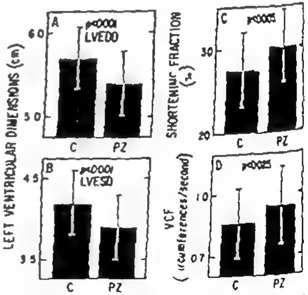
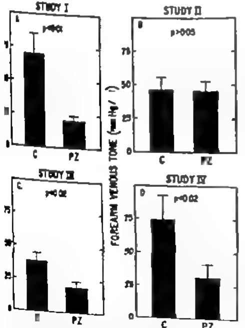


Figure 3 Echographic evaluation of the cardiac effects of long-term prazosin (PZ) therapy (2–7 mg, four times daily) in chronic CHF due to coronary disease two weeks after initiation of ambulatory therapy (PZ) compared to control (C) on left ventricular end-diastolic dimension (LVEDD, panel A), left ventricular end-systolic dimension (LVESD, panel B), left ventricular shortening fraction (panel C) and on mean rate of left ventricular circumferential fiber shortening (VCF panel D)

vasodilator agent from 0.60±0.09 to 1.11±0.14 ml/100 gm/min (p<0.001). Meanwhile FVR was decreased from 165.6±24.4 to 93.9±18.0 mm Hg/ml/100 gm/min (p<0.001) (Figure 6A) and forearm venous tone was diminished from 38.8±6.3 to ..4.4 mm Hg/ml (p<0.001) (Figure 6B).

...dditionally following a two week period of interruption in continuous oral prazosin therapy the administration of a dose of prazosin identical with doses ... in Study I showed return of beneficial peripheral ...lar reducing effects of the vasodilator agent. Thus, ...rm blood flow was improved from 0.82±0.16 to ...±0.14 ml/100 gm/min while FVR declined from ...±30.1 to 120.6±28.7 mm Hg/ml/100 gm/min (Figure 6A) and FVT decreased from 74.4±19.2 to ...±9.6 mm Hg/ml (Figure 6B) (all p<0.001).

...es although continuous ambulatory therapy of ... with prazosin is associated with blunting of the ... impedance and preload reducing actions of the ..., these benefits are restored by either the administration of a higher dose or interrupted therapy ... prazosin.



...re 6B. Action of prazosin (PZ) on forearm venous tone (FVT). Studies I through IV represent initial, chronic, higher ..., and uninterrupted PZ responses as in Figure 6A. C ...ontrol.

SEQUENTIAL ACUTE SUBACUTE AND LATE HEMODYNAMIC EVALUATION

To evaluate the clinical significance of "acute hemodynamic tachyphylaxis" 7 patients with severe chronic CHF underwent sequential acute, subacute and late hemodynamic evaluation during constant dose (5 mg q.i.d.) uninterrupted oral prazosin therapy. The first dose of prazosin modestly decreased mean systemic blood pressure (Figure 7, panel A, Day 1) from 78 to 69 mm Hg (p<0.05), while cardiac index (panel B) rose markedly from 2.1 to 2.6 l/min/m^2 (p<0.01) and left ventricular filling pressure (panel C) declined

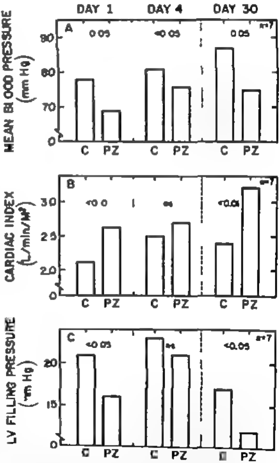


Figure 7. Sequential hemodynamic actions of prazosin (PZ): acute (Day 1), subacute (Day 4), and late (Day 30) on mean blood pressure (panel A), cardiac index (panel B), and left ventricular (LV) filling pressure during continuous uninterrupted PZ (5 mg q.i.d.) therapy of CHF.

tained improved with 12 months of prazosin therapy (Figure 5).

DELAYED PRAZOSIN TOLERANCE

During the course of follow up of a large series of patients with severe CHF we noted gradually increasing prazosin dosage requirements in some patients. While this finding may be related to gradual deterioration of ventricular function the development of tolerance to the systemic vasodilator actions of prazosin was considered. Therefore, a series of sequential plethysmographic investigations (Awan *et al* 1978) of peripheral vasodilator actions of the agent was undertaken in our laboratories (Figures 6A and 6B).

Following measurement of control plethysmographic variables prazosin 2–7 mg was administered (Study I) and plethysmographic variables were remeasured at 30 minutes and 60 minutes post prazosin. In Study II an identical dose of prazosin was administered and control and post prazosin plethysmographic recordings were made. For Study III prazosin 6–14 mg (8.4±2.1 mg) was ingested and for Study IV following a two week interruption of prazosin treatment the same dose as in Study I (3.9±8 mg) was administered for plethysmographic studies.

Study I (Richardson *et al* 1958) demonstrated that in these patients forearm blood flow (FBF) increased from 1.25±0.23 to 1.62±0.31 ml/100 gm/min ($p<0.01$) with prazosin while forearm vascular resistance declined from 90.8±10.5 to 43.5±13 mm Hg/ml/100 gm/min ($p<0.001$) (Figure 6A) and forearm venous tone (FVT) decreased from 69.5±14.9 to 20.7±3.0 mm Hg/ml ($p<0.01$) (Figure 6B).

Study II performed six months following initiation of continuous therapy with oral prazosin four times daily showed that the vasodilator agent produced no significant change from control in FBF, FVR or FVT ($p>0.05$).

Study III using higher prazosin dosage demonstrated that beneficial peripheral vascular dilating effects of prazosin were restored. Thus FBF was elevated by

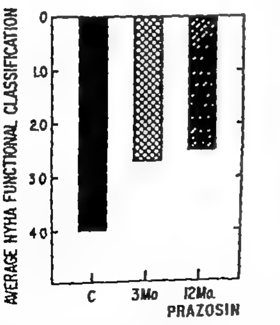


Figure 5. Efficacy of oral prazosin (2–7 mg, four times daily) on chronic CHF symptoms in coronary patients at 3 months and 12 months of continuous prazosin therapy. The NYHA functional class is indicated by numerals 1–4 during control and with prazosin.

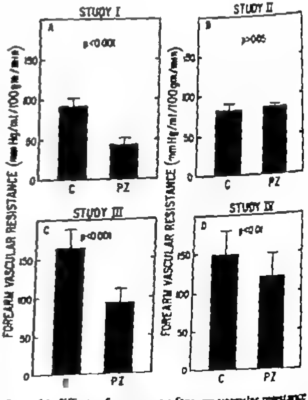


Figure 6A. Effects of prazosin on forearm vascular resistance (FVR). Study I describes effect of initial prazosin (PZ) dose. Study II represents effect of same dose on FVR after 3 months of uninterrupted PZ therapy. Study III represents the effect of higher dose PZ on FVR. Study IV describes effect of PZ on FVR following a 2 week period of interruption of PZ therapy. C = control.

vasodilator agent from 0.60±0.09 to 1.11±0.14 ml/100 gm/min (p<0.001). Meanwhile FVR was de- creased from 165.6±24.4 to 93.9±18.0 mm Hg/ml/100 gm/min (p<0.001) (Figure 6A) and fore- arm venous tone was diminished from 38.8±6.3 to ±4.4 mm Hg/ml (p<0.001) (Figure 6B).

Additionally, following a two week period of inter- ruption in continuous oral prazosin therapy, the ad- ministration of a dose of prazosin identical with doses used in Study I showed return of beneficial peripheral vascular relaxing effects of the vasodilator agent. Thus, forearm blood flow was improved from 0.82±0.16 to 1.5±0.14 ml/100 gm/min while FVR declined from 2±30.1 to 120.6±28.7 mm Hg/ml/100 gm/min (Figure 6A) and FVT decreased from 74.4±19.2 to 7±9.6 mm Hg/ml (Figure 6B) (all p<0.001).

Thus although continuous ambulatory therapy of CHF with prazosin is associated with blunting of the impedance and preload reducing actions of the agent, these benefits are restored by either the administration of a higher dose or interrupted therapy with prazosin.

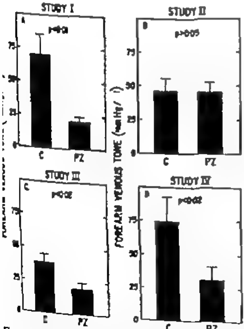


Figure 6B. Action of prazosin (PZ) on forearm venous tone (FVT). Studies I through IV represent usual, chronic, higher dose, and uninterrupted PZ responses as in Figure 6A. C = control.

SEQUENTIAL ACUTE SUBACUTE AND LATE HEMODYNAMIC EVALUATION

To evaluate the clinical significance of "acute hemodynamic tachyphylaxis" 7 patients with severe chronic CHF underwent sequential acute, subacute and late hemodynamic evaluation during constant dose (5 mg q.i.d.) uninterrupted oral prazosin therapy. The first dose of prazosin modestly decreased mean systemic blood pressure (Figure 7, panel A, Day 1) from 78 to 69 mm Hg (p<0.05), while cardiac index (panel B) rose markedly from 2.1 to 2.6 $l/min/m^2$ (p<0.01) and left ventricular filling pressure (panel C) declined

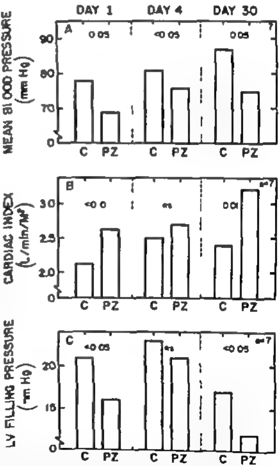


Figure 7. Sequential hemodynamic actions of prazosin (PZ): acute (Day 1), subacute (Day 4), and late (Day 30) on mean blood pressure (panel A), cardiac index (panel B), and left ventricular (LV) filling pressure during continuous uninterrupted PZ (5 mg q.i.d.) therapy of CHF.

from 21 to 16 mm Hg ($p<0.05$). Following continuous therapy with prazosin (5 mg orally q.i.d.), on Day 4 (Figure 7) the fifteenth dose of oral prazosin was accompanied by attenuated hemodynamic responses. Thus mean blood pressure (panel A) diminished only from 81 to 76 mm Hg ($p<0.05$) whereas the control cardiac index (panel B) of 2.5 was 2.7 $l/min/m^2$ ($p<0.05$) after prazosin and the control left ventricular filling pressure (panel C) of 23 was 21 mm Hg ($p>0.05$) after prazosin. However, with further uninterrupted prazosin therapy (constant dose 5 mg orally q.i.d.) repeat evaluation on day 30 (Figure 7) demonstrated spontaneous restoration of salutary hemodynamic effects. Prazosin lowered the control mean blood pressure (panel A) of 87 to 75 mm Hg ($p<0.05$), concomitantly augmenting the control cardiac index (panel B) of 2.4 to 3.2 $l/min/m^2$ ($p<0.01$) and reducing control left ventricular filling pressure (panel C) of 17 to 12 mm Hg ($p<0.05$).

COMMENTS

Our investigations of the circulatory effects of prazosin demonstrate that the vasodilator exerts a rapid and prolonged dilating action on both the arterial and venous systems (Figures 2–4) (Awan *et al.* 1977[a], Miller *et al.* 1977, Awan *et al.* 1977[b]). Plethysmographic studies from our laboratories demonstrate that oral prazosin has systemic vasodilator effects comparable to those of parenteral nitroprusside (Awan *et al.* 1977[a], Awan *et al.* 1978). Further, we have shown by direct hemodynamic measurements that these peripheral circulatory actions of oral prazosin are similar to nitroprusside and, like the latter agent, are translated into dramatic improvements in markedly deranged cardiac dynamics in patients with chronic ischemic CHF (Awan *et al.* 1977[a, b], Miller *et al.* 1977, Awan *et al.* 1978). As a result, there are nitroprusside-like (Figure 1) salutary effects on both left ventricular filling pressure and CO (Awan *et al.* 1977[b], Miller *et al.* 1977, Awan *et al.* 1978). Thus, prazosin is unique among oral vasodilator agents in possessing combined effects on both aortic impedance and cardiac preload (Awan *et al.* 1977[b], Miller *et al.* 1977, Awan *et al.* 1978).

Of great significance is our finding that impedance and preload reduction induced by the new systemic oral vasodilator prazosin, markedly enhances cardiac performance in patients with severe left ventricular failure persisting despite treatment with digoxin and diuretics. It is pointed out that this salutary effect occurred when prazosin was substituted for long-acting nitrates. Thus, by such an addition of prazosin to the therapeutic regimen, concomitant with improvements in hemodynamic (Figures 1 and 2) and echographic (Figures 3 and 4) variables of ventricular function, exercise testing demonstrated increased functional capacity characterized by prolongation of physical activity and increased maximal body oxygen consumption, whereas cardiac efficiency increased. In addition to these objective measures of enhanced pump activity, all patients experienced substantial benefit in functional classification indicated by lessened fatigue and dyspnea (Figure 5). Thereby, the incorporation of prazosin into conventional CHF therapy permitted symptomatically incapacitated patients to perform at least moderate physical exertion (Awan *et al.* 1977[b]).

The hemodynamic (Figures 1 and 2) and echocardiographic (Figures 3 and 4) observations in the present series of patients indicate that the beneficial symptomatic effects of prazosin resulted from relatively equal vasodilator actions of the drug on the systemic arterial and venous beds, such that peripheral arteriolodilation produced a decrease in aortic impedance whereas venodilation promoted systemic venous pooling. The former action caused enhanced ventricular emptying so that the lowered ejection fraction was raised (Figure 3C), whereas the latter action resulted in a decline of venous return to the heart with a decrease in diastolic cardiac chamber volume (Figures 3A and 4) and relief of pulmonary congestion (Awan *et al.* 1977[b]). These effects of oral prazosin therapy were exemplified by reduction in systemic vascular resistance (Figure 2C) and diminution in intraventricular echographic dimensions (Figures 3A, 3B and 4). The enhanced CO (Figure 1C) combined with the decrease in increased left ventricular filling pressure (Figure 1B) afforded by prazosin thereby permitted increased exercise tolerance with less inducement of fatigue and dyspnea (Figure 5).

During the phase of extended follow up on continuous prazosin therapy we noticed that while the majority of our CHF patients continued to maintain considerably improved symptomatology with a con-

nt dose of prazosin, approximately 30 % of the patients required a higher dose of this systemic vasodilator to produce unaltered relief of symptoms. To determine whether this represented deteriorating ventricular function in some patients or delayed vasodilator tolerance to prazosin, we performed serial peripheral vascular studies (Awan *et al.* 1978) in patients requiring the higher prazosin doses. Study I (Figure 6A and 6B) was the initial plethysmographic study performed on first exposure to prazosin. It is noteworthy that prazosin typically caused dramatic decline in forearm vascular resistance and forearm venous tone when first administered to the patients. However when the patients who demonstrated higher prazosin requirements were retested (Study II) with the initial prazosin dose employed in Study I, there was no significant change in vascular resistance or venous tone. Nevertheless when the higher currently symptomatically effective dose of prazosin was tested (Study III, Figures 6A and 6B) beneficial vasodilator responses were again observed. Thus, it is not deterioration of cardiac function which contributes to the blunting of vasodilator responses to prazosin in a third of severe CHF patients treated long-term with this vasorelaxant drug but rather the development of true vasodilator tolerance. This tolerance can be minimized by increasing the prazosin dose (Figure 6A and 6B, Study III) or by temporary interruption of prazosin therapy (Study IV, Figures 6A and 6B).

The mechanism of this delayed vasodilator tolerance to prazosin remains conjectural but has also been noted with other vasodilators such as long acting nitrates (Mantle *et al.* 1979) and oral hydralazine (Packer *et al.* 1980). Secondary hyperaldosteronism often exists in severe chronic CHF (Brown *et al.* 1970, Watkins *et al.* 1976) and by lowering intracardiac pressures vasodilator agents may accentuate renin and aldosterone levels, thereby exacerbating sodium retention. The resulting edema of the blood vessels may cause diminished circulatory responsiveness (Zelis *et al.* 1963) to the systemic vasodilator agents. In this regard, we have observed that increased dose of diuretics, combination diuretic therapy and the use of spironolactone "priming" before prolonged vasodilator therapy in CHF patients largely obviates delayed vasodilator tolerance to prazosin.

The more recently described phenomenon of subacute attenuation of the hemodynamic effects of prazosin (Arnold *et al.* 1979, Elkayam *et al.* 1979, Packer *et al.* 1979) inappropriately labelled "tachyphylaxis" is perhaps not as enigmatic as we have been led to believe. Prazosin is an alpha 1 (vascular post-synaptic) receptor blocking agent without significant action on the alpha 2 (neuronal ending; pre synaptic) receptor (Davey *et al.* 1977). Thus prazosin effected alpha 1 receptor blockade leaves the function of the alpha 2 receptor undisturbed. Thereby the neuronal ending continues secretion of its neurohumoral transmitter noradrenaline, in an effort to maintain vascular tone (Kalsner & Chan 1979). However since the alpha-1 receptor is blocked by prazosin, the noradrenaline level builds in the presynaptic area and finally causes stimulation of the alpha-2 receptor leading to reduction of noradrenaline secretion (Graham & Peltinger 1979). If this hypothesis is correct it would be anticipated that prazosin would initially cause profound vasodilation with beneficial augmentation of cardiac function in CHF patients. However increased noradrenaline secretion from the neuronal ending would rapidly and progressively blunt this vasodilation. Finally the stimulation of the alpha-2 receptor with "turning off" of the noradrenaline would unmask continued beneficial prazosin effected salutary vasodilation. In this regard, it is highly relevant that while acute hemodynamic responses to prazosin are generally recognized to be beneficial (Awan *et al.* 1977[a], Miller *et al.* 1977, Awan *et al.* 1978) and subacute attenuation is reported (Arnold *et al.* 1979, Elkayam *et al.* 1979, Packer *et al.* 1979), all presently available long term studies have described significantly beneficial effects of prazosin on hemodynamics, scintigraphic ejection fractions, exercise tolerance and symptomatology (Awan *et al.* 1977[b], Colucci *et al.* 1980, Bertel 1980 among others – see reference list). To provide further clarification of these phenomena we sequentially examined prazosin effects acutely, subacutely and following long-term therapy in several patients with severe chronic CHF. During initial exposure to the drug (Figure 7), prazosin modestly reduced blood pressure, while markedly augmenting CO and substantially diminishing left ventricular preload. Thereafter the patients were started on prazosin 5 mg orally four times daily and underwent hemo-

dynamic re-evaluation on Day 4 after the fifteenth dose of prazosin As demonstrated in Figure 7 the vasodilator effects of prazosin were considerably attenuated with mild reduction in blood pressure but no change in pump output or left ventricular filling pressure Nevertheless we maintained each of our patients on a constant dose of prazosin (5 mg orally q i d) and performed an additional third evaluation by cardiac catheterization on Day 30 of continuous therapy with this vasodilator (Figure 7). Remarkably at this evaluation there was no evidence of hemodynamic attenuation of prazosin effects with significant post prazosin declines in blood pressure and left ventricular filling pressure, and marked increase in CO being demonstrated Coincidentally our patients described major improvement in symptomatology and were confirmed to have a substantial increase in exercise tolerance.

Our findings in this ongoing study of the sustained actions of oral prazosin confirm and emphasize the triphasic nature of hemodynamic responses to alpha 1 receptor blockade with this vasodilator in patients with severe chronic CHF Thus, despite subacute blunting of prazosin effects acutely observed beneficial actions of prazosin were predictive of continued long term salutary actions of this vasodilator in patients with left ventricular failure. Our findings also underscore the transient character of subacute hemodynamic blunting. Moreover since this subacute phenomenon is neither complete nor final the use of the term "tachyphylaxis" to describe subacute blunting represents an inaccurate, misleading and hasty misnomer

In conclusion, experience at the University of California Davis, indicates that the oral quinazoline derivative prazosin is extremely beneficial for the sustained ambulatory management of patients with severe chronic CHF refractory to optimal doses of digoxin and diuretics Prazosin produced salutary augmentation of left ventricular pump function results in enhanced exercise tolerance with diminished heart failure symptomatology Although delayed vasodilator tolerance occurs in approximately a third of the patients, it can be considerably prevented by prior dosing with aldosteroneantagonist agents and conveniently treated with the addition of the latter drugs increased diuretic dosage or temporary substitution vasodilator therapy Subacute hemodynamic suppression of prazosin beneficial responses is a transient phenomenon which does not preclude substantial sustained salutary vasodilator actions of prazosin in patients with severe CHF

SUMMARY

The cardiocirculatory actions of the oral vasodilator prazosin, were evaluated by cardiac catheterization, forearm plethysmography echocardiography treadmill exercise, and symptoms in patients with advanced longstanding CHF Oral prazosin (2 to 7 mg) reduced forearm venous tone and decreased forearm vascular resistance. Concomitantly mean systemic arterial pressure declined, left ventricular filling pressure decreased, and cardiac index was raised. These effects of a single dose of prazosin on left ventricular function were rapid in onset, maximal at 1 hour and sustained for the entire 6 hour period of observation. After two weeks of outpatient therapy with 2 to 7 mg prazosin four times daily echographic end-diastolic dimension decreased whereas the duration of treadmill exercise increased Symptoms (dyspnea, fatigue, angina) were diminished throughout the course of prazosin therapy and New York Heart Association functional class improved from 3 7 to 2.2. Thus, prazosin possesses sustained nitroprusside-like balanced dilator actions on the systemic arterial and venous beds, which are effectively translated into beneficial hemodynamics of augmenting lowered CO and relieving excessive left ventricular end-diastolic pressure Delayed vasodilator tolerance occurring in 30 % patients is prevented by prior use of aldosterone antagonists and is easily treated. Subacute hemodynamic suppression of beneficial prazosin vasodilator actions is transient and does not preclude successful sustained prazosin therapy of severe heart failure

The quinazoline, derivative, prazosin, is a new oral vasodilator antihypertensive agent structurally unrelated to other antihypertensive agents available in the United States (Richardson *et al* 1958 Cohen 1970, Constantine *et al* 1973 Constantine *et al* 1975 Hess 1975). It has major peripheral vascular relaxing effects produced by post synaptic alpha blockade (Richardson *et al* 1958 Cohen 1970 Constantine *et al* 1973 Con-

stantine *et al.* 1975 Hess 1975) The clinical efficacy of prazosin was therefore evaluated at our institution in a series of investigations designed to assess the cardiocirculatory actions of the agent (Awan *et al.* 1977[a] Miller *et al.* 1977 Awan *et al.* 1977[b] Awan *et al.* 1978), and the resultant hemodynamic effects of the long term administration of this vasodilator on an outpatient basis relative to symptoms, functional capacity and exercise tolerance in ambulatory patients with severe chronic CHF intractable to digoxin, diuretics and nitrates.

Acknowledgement
We gratefully acknowledge the technical assistance of Ray Drahun

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NITROPRUSSIDE INFUSION IN ACUTE MYOCARDIAL INFARCTION

Jay N. Cohn, Joseph A. Franciosa and Gary S. Francis

In 1971 we reported that patients with acute myocardial infarction (AMI) usually exhibited an elevated left ventricular end-diastolic pressure and frequently a reduction in stroke volume (SV) and cardiac output (CO) during the acute phase of the illness (Hamosh & Cohn 1971). This left ventricular dysfunction often was not accompanied by any other signs or symptoms of congestive heart failure (CHF). Since an elevated left ventricular diastolic pressure may impair subendocardial perfusion (Buckberg *et al.* 1972), particularly in the presence of coronary artery disease, and a low SV may be an early harbinger of shock (Cohn & Franciosa 1973), we entertained the possibility that this hemodynamic evidence of left ventricular dysfunction might be a contributor to progressive myocardial ischemia and pump failure.

In 1972 we reported that infusion of the vasodilator sodium nitroprusside markedly improved left ventricular pump function in the setting of AMI with a fall in the elevated left ventricular end-diastolic pressure and a rise in SV and CO (Franciosa *et al.* 1971). Since this improvement in left ventricular performance was accompanied by a modest fall in systemic arterial pressure it was apparent that the benefit:risk ratio of this intervention had to be clearly established. Furthermore, the availability of an intravenous drug that could immediately improve the impaired performance of the left ventricle made it possible to test the hypothesis that the pump dysfunction contributed to the morbidity and mortality of AMI. Consequently, in 1974 a Cooperative Study was undertaken involving 10 Veterans Administration Hospitals in the United States. The goal of this study was to evaluate the efficacy of a 48 hour infusion of sodium nitroprusside in patients with AMI complicated by left ventricular dysfunction. The final results of this multicenter trial are not available since the trial is just now drawing to a conclusion. Nonetheless, experience obtained during this carefully controlled study has led to a better understanding of the disease process and the hemodynamic effects of the drug.

Over 800 patients have been randomized in this controlled trial, with half being assigned double-blind to infusion of placebo and the other half to infusion of sodium nitroprusside. The protocol called for the gradual titration of the drug infusion until pulmonary wedge pressure was reduced by 40 % from its initially elevated levels of greater than 12 mm Hg or until arterial pressure fell below a predetermined systolic level or until an infusion rate of 200 mg/min of nitroprusside or a comparable infusion rate of placebo was attained. All patients required a pulmonary artery catheter for monitoring of pulmonary artery pressure and this was accomplished in over 95 % of patients in whom it was attempted. The therapeutic goal of a 40 % reduction of pulmonary wedge pressure was achieved in 70 % of the patients who received nitroprusside but only 5 % receiving placebo. Furthermore, pulmonary artery wedge pressure was maintained at constant levels during the 48 hour period of infusion in the patients received nitroprusside, findings indicative of the stable hemodynamic response to this drug. The placebo treated patients also exhibited a fall in pulmonary wedge pressure which occurred progressively during the 48 hour monitoring. Indeed, the pulmonary artery wedge pressure in the placebo and nitroprusside groups reached the same level about 40 hours after the infusion was begun. Thereafter the placebo group actually exhibited a lower pulmonary wedge pressure. This marked reduction in wedge pressure in the placebo group could in part be related to the natural history of the disease process but also may have been influenced by the administration of diuretics, which were given more frequently in the

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placebo group than in the nitroprusside group because of the early fall in wedge pressure induced by nitroprusside in the treated patients.

The fall in arterial pressure induced by nitroprusside was well tolerated and in only rare instances was it necessary to discontinue the infusion of the active drug. Since both arterial diastolic and pulmonary wedge pressure fell in response to nitroprusside the effect on effective perfusion pressure of the left ventricle, that is arterial diastolic minus pulmonary wedge pressure was only modest. This effective perfusion pressure remained lower in the nitroprusside group than in the placebo treated group by about 4 mm Hg during the early phase of the 48 hour infusion but tended to equalize by the end of the infusion.

A wide variety of clinical and laboratory data have been collected as part of this control trial. Multiple blood samples for analysis of CK MB isoenzyme and calculation of enzymatic infarct size have been obtained during the early phase of the illness (Sobel *et al* 1972). Chest x rays have been obtained at regular intervals and are being reviewed blindly by a single radiologist. Twentyfour hour tape recordings of the electrocardiogram have been obtained during the first day and the 14th day of the illness. The requirement for concomitant drug administration including the use of narcotics has been carefully assessed. Side effects of the therapy have been closely monitored. Clinical findings at the time of discharge in the two groups of patients have been evaluated and follow-up examinations have been performed at 7 and 13 weeks after the acute event. Finally exercise testing to assess exercise capacity has been carried out in all patients at 13 weeks and the mortality rate at one year is being followed.

The effects of this 48 hour infusion on mortality in AMI will not be known until careful assessment of the overall data and analysis of drug effect in specific subsets has been carefully reviewed. Nonetheless certain observations made during the course of the study allow some early conclusions:

1) Catheterization of the pulmonary artery in the setting of AMI can be accomplished with a very high success rate and a very low morbidity rate.

2) Clinical findings of left ventricular failure are poor indices of the pulmonary wedge pressure. Therefore hemodynamic measurements in the setting of AMI provide different information than bedside assessment and this information may be valuable in choosing therapy for an individual patient.

3) A 48-hour infusion of sodium nitroprusside can be administered without undue difficulty in AMI and the hemodynamic response to this therapy is stable once the drug has been titrated.

4) Side effects during infusion of this drug are minor and rarely require cessation of therapy.

5) The reduction in arterial pressure induced by infusion of sodium nitroprusside is accompanied by a fall in pulmonary wedge pressure and results in only a very slight reduction in the effective perfusion pressure of the subendocardium.

6) Even in the absence of vasodilator therapy pulmonary wedge pressure falls progressively during the first 48 hours after AMI. The role of diuretics in this response remains uncertain.

7) The beneficial hemodynamic effects of sodium nitroprusside in AMI is well-established and an acute salutary effect on clinical signs of CHF is frequently observed. Until final results of this study are made available for analysis use of this drug in the setting of pump failure accompanying AMI should not be based on any assumed long-term beneficial effects. Nonetheless, early data from this study suggest that the potential benefits of this therapy can be obtained at a relatively low risk and therefore cautious use in appropriate clinical settings may be justified.

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DISCUSSION

Johansson.

You seem to be disappointed on the lack of correlation between the occurrence of an elevated wedge pressure and clinical signs. The protocol also included auscultation of a third heart sound. Was the relation better between this finding and a raised left ventricular filling pressure.

Cohn.

The third heart sound did not help. I do not know if I am disappointed or delighted about this poor correlation The difference in opinion between different examiners about physical findings is so large that I worry about how much reliance one can place upon such data None of the clinical signs and also the chest X ray were very helpful.

Johansson:

If you break down the mortality into subgroups: sudden death, re-infarction and so on could you predict from the haemodynamic findings which of the patients would die a sudden death and who would die from a re infarction.

Cohn

We do not have enough data yet about the haemodynamic course in those who survive and those who die from either sudden death or pump failure At the moment it is clear that there is a subset of patients whose wedge pressure does not fall These patients do indeed seem to have a bad prognosis It is also interesting and one thing to really learn from this study that the mortality rate in hospital was far below the one predicted. When we started we predicted a mortality rate of about 30 % given the overall mortality rate in myocardial infarction and the fact the patients without CHF rarely die in hospital We thought that our subset was going to have about a 30–40 % mortality rate. Indeed the in-hospital mortality rate in 21 days was much lower than that The mortality rate after they left hospital from 21 days to 13 weeks was extraordinary high Most suffered sudden death, perhaps re-infarction. What we learned was that coronary care have markedly reduced in-hospital mortality Subsequently at home they die and if we are going to have an impact upon total mortality it has to be on the out of hospital mortality and not the in-hospital mortality

PHENTOLAMINE IN ACUTE MYOCARDIAL INFARCTION HEMODYNAMIC AND METABOLIC EFFECTS

Kanu Chatterjee and William W. Parmley

INTRODUCTION

Changes in left ventricular outflow resistance profoundly alter cardiac performance (Chatterjee & Parmley 1976, Mason 1975, Sonnenblick 1962); an increased resistance is associated with a decrease in forward stroke volume (SV) and cardiac output (CO) and an increase in left ventricular diastolic volume and pressure. A reduction in outflow resistance, on the other hand, causes an increase in left ventricular forward SV and CO, reduction in left ventricular end-diastolic volume and pressure. This principle of reduction of left ventricular outflow resistance with the use of vasodilator agents to enhance cardiac performance in patients with acute and chronic CHF has now been applied clinically. A number of vasodilator agents have the potential to improve cardiac performance of patients with acute and chronic CHF (Chatterjee & Parmley 1976, Chatterjee *et al* 1973, Chatterjee & Swan 1974, Williams *et al* 1975). Although phentolamine is an alpha-adrenergic blocking agent, it also directly relaxes the smooth muscle of the arteries and veins (Abboud *et al* 1968). Due to arteriolar dilatation, a reduction in systemic vascular resistance is observed. As systemic vascular resistance forms a major component of the total left ventricular outflow resistance, it is associated with an increase in SV and CO. Phentolamine-induced peripheral venodilatation may also produce beneficial effects. Reduction of intracardiac volume and pressure is associated with a decrease in pulmonary and systemic venous pressure. These major hemodynamic effects of phentolamine have the potential to alleviate the signs and symptoms of heart failure. Indeed, the beneficial hemodynamic and clinical effects of phentolamine have been documented in patients with chronic CHF with or without valvular disease (Gould *et al* 1969, Majid *et al* 1971). Phentolamine has also been used for the treatment of pump failure complicating acute myocardial infarction (AMI) (Gould *et al* 1974, Kelly *et al* 1973, Perret *et al* 1975, Walinsky *et al.* 1974).

HEMODYNAMIC EFFECTS OF INTRAVENOUS PHENTOLAMINE IN ACUTE MYOCARDIAL INFARCTION

The hemodynamic effects of intravenous phentolamine in patients with AMI have been evaluated in a number of studies (Gould *et al* 1974, Kelly *et al* 1973, Perret *et al* 1975, Walinsky *et al* 1974). The hemodynamic effects were characterized by a decrease in left ventricular filling pressure, mean arterial pressure, and systemic and pulmonary vascular resistances. Right atrial pressure also decreased in the majority of patients. The changes in CO and SV and left ventricular performance were influenced by the presence or absence of left ventricular failure and the initial level of left ventricular filling pressure. The differences in hemodynamic response to phentolamine infusion in patients with left ventricular failure and elevated left ventricular filling pressure (Group A) from those without left ventricular failure and normal left ventricular filling pressure (Group B) are summarized in Table 1. In patients without left ventricular failure and normal initial left ventricular filling pressure, there was a significant increase in heart rate during phentolamine infusion. However, in patients with left ventricular failure, tachycardia did not develop. Mean systemic arterial and pulmonary arterial pressures fell in both groups. Pulmonary vascular resistance decreased significantly only in Group A patients. In patients with left ventricular failure (Group A), along with the decrease in systemic vascular resistance, there was a significant increase in CO. However, CO remained unchanged in patients without left ventricular failure, although there was a modest decrease in systemic vascular resistance. Left ventricular filling pressure decreased significantly irrespective of the initial level of left ventricular filling pressure; however, stroke vo-

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Table I Hemodynamic effects of phentolamine in acute myocardial infarction in patients (Group A) with increased left ventricular filling pressure and patients (Group B) with normal left ventricular filling pressure

	Group A			Group B		
	Pre	Post	P	Pre	Post	P
HR (beats/min)	94.2±5.8	99.8±7.0	NS	77±4.6	94±7.1	0.05
MAP (mm Hg)	98.8±5.7	74.7±5.1	0.0005	94±2.4	83±4.6	0.05
LVFP (mm Hg)	23.9±2.8	13.6±2.3	0.005	11±1.1	6±0.7	0.005
CI (L/min/m²)	2.1±0.2	2.9±0.4	0.005	2.5±0.25	2.6±0.33	NS
SVI (ml/m²)	22.5±1.9	29.3±3.2	0.005	32±3.2	26±2.5	0.005
SWI (g m/m²)	31.0±3.8	30.1±3.7	NS	42±4.7	32±4.2	0.005
SVR (dynes sec cm⁻⁵)	2192±260	1377±262	0.0005	1668±157	1414±109	0.02
PVR (dynes sec cm⁻⁵)	474±124	271±63	0.0005	103±24	89±14	NS
MPAP (mm Hg)	31.1±3.0	21.4±2.1	0.0005	16±1.7	12±0.2	0.05

HR = heart rate, MAP = mean arterial pressure, LVFP = left ventricular filling pressure, CI = cardiac index, SVI stroke volume index, SWI = stroke work index, SVR = systemic vascular resistance, PVR = pulmonary vascular resistance, MPAP = mean pulmonary artery pressure (NS = not significant)

lume index increased only in patients with left ventricular failure and high initial left ventricular filling pressure. In Group B patients, stroke volume index actually decreased. The relative changes in various hemodynamic variables in patients with and without left ventricular failure are illustrated in Figure 1. In patients without left ventricular failure, heart rate increased by an average of 40 %. Whereas, in patients with left ventricular failure, increase in heart rate was minimal. Left ventricular filling pressure decreased by similar magnitude (80 %) in both groups of patients. Cardiac output and stroke volume index increased by an average of 60 % in patients with left ventricular failure, in contrast, in patients without left ventricular failure stroke volume index decreased by approximately 30 %. Improved left ventricular performance during phentolamine infusion was noted only in patients whose left ventricular filling pressure was initially elevated (Figure 2) (next page)

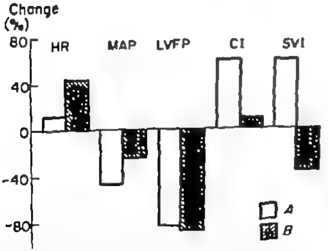

Figure 1 Percentage changes from the control values in heart rate, mean arterial pressure (MAP), left ventricular filling pressure (LVFP), cardiac index (CI) and stroke volume index (SVI) in patients with (open bar) and without (hashed bar) failure during phentolamine infusion. Increase in heart rate was observed in patients without failure. Increase in cardiac index and stroke volume index was observed in patients with failure, although left ventricular filling pressure decreased in both groups

CHANGES IN CORONARY HEMODYNAMICS

It is relevant and clinically important to evaluate changes in coronary hemodynamics and myocardial metabolic function in patients with AMI during phentolamine infusion because of the potential risk of enhancing myocardial ischemia. During phentolamine infusion, there is usually some reduction in arterial pressure, coronary blood flow therefore, may decrease. Furthermore phentolamine tends to induce a tachycardia. Such an increase in heart rate may not only increase myocardial oxygen demand, but also may compromise myocardial perfusion due to a reduction in diastolic perfusion time. Recent studies in animals

without heart failure indicate that phentolamine may enhance inotropism indirectly by causing increased synthesis and release of cardiac norepinephrine, presumably due to receptor blockade (Bagwell *et al* 1970, Darmon *et al* 1968, Ramanathan *et al* 1975 Sing *et al* 1970, Zahr *et al* 1971) Therefore, the potential deleterious effects of phentolamine infusion in patients with AMI must be considered Phentolamine, however also causes a significant reduction in left ventricular end-diastolic pressure, along with a decrease in left ventricular systolic pressure. Thus, left ventricular wall tension, a major determinant of myocardial oxygen demand may decrease during phentolamine infusion The net effect on coronary hemodynamics and myocardial metabolism, therefore, is likely to be influenced not only by the changes in the determinants of myocardial perfusion, but also by the concomitant changes in myocardial oxygen demand Gould *et al* (1975) observed a significant increase in overall myocardial blood flow in patients with AMI during phentolamine infusion This increase in myocardial blood flow was observed despite a fall in arterial and left ventricular filling pressure Although it was assumed that this increase in coronary blood flow was related to phentolamine induced primary decrease in coronary vascular resistance, the potential role of possible increase in the contractile state was not evaluated in this study Most patients also developed tachycardia which might also have been contributory

Changes in coronary hemodynamics and myocardial oxygen consumption during phentolamine infu

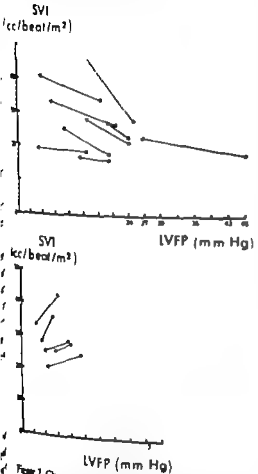

Figure 2 Changes in stroke volume index (SVI) on vertical axis and left ventricular filling pressure (LVFP) on a horizontal axis during phentolamine infusion in patients with left ventricular failure (upper panel) and without left ventricular failure (lower panel) Solid circles indicate the initial values and the arrows indicate changes during phentolamine infusion. In patients with left ventricular failure there was an increase in stroke volume index along with a decrease in left ventricular filling pressure, indicating improved left ventricular performance In contrast, in patients without left ventricular failure, stroke volume index decreased along with the further fall in left ventricular filling pressure, indicating an impairment in cardiac function

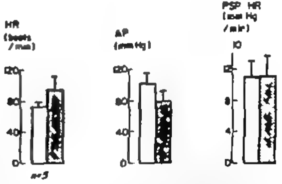

Figure 3 Changes in heart rate (HR), peak systolic pressure (PA) and in the product of peak systolic pressure and heart rate (PSP HR) during phentolamine infusion in patients with left ventricular failure complicating acute myocardial infarction There was modest increase in heart rate with concomitant fall in peak systolic pressure The product of peak systolic pressure and heart rate did not change Open bar = control values, hashed bar = values during phentolamine infusion

sion in a group of patients with AMI complicated by left ventricular failure are illustrated in Figures 3 to 6 In these patients there was a slight increase in heart rate, but arterial pressure also fell The produce of peak systolic pressure and heart rate a frequently used index of myocardial oxygen demand did not change (Figure 3) The coronary sinus blood flow an approximation of myocardial blood flow and the arterial coronary sinus oxygen content difference and their products that is myocardial oxygen consumption, also remained unchanged (Figure 4 & 5). Cardiac output however increased significantly along with a fall in left ventricular filling pressure suggesting improved left ventricular performance (Figure 6). Thus in these patients, enhanced cardiac performance occurred with little or no increase in myocardial oxygen consumption. These findings indicate that with phentolamine the improvement in mechanical performance of the left ventricle may not be associated with any deleterious effects on overall myocardial metabolic function in patients with AMI complicated by left ventricular failure.

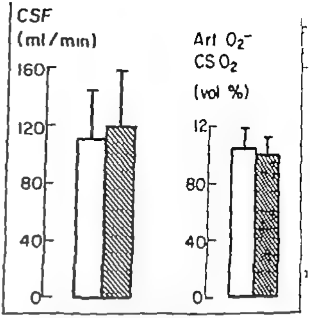

Figure 4 Changes in coronary sinus flow (CSF) and arterial coronary sinus oxygen content difference (arterial O_2 coronary sinus O_2) during phentolamine infusion Open bar control values; hashed bar = values obtained during phentolamine infusion Coronary sinus flow and arterial coronary sinus oxygen content difference did not change in these patients during phentolamine infusion

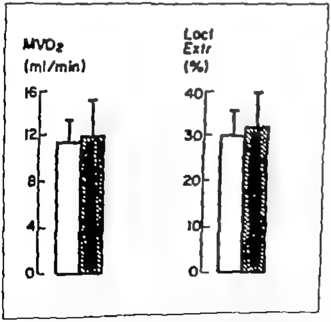

Figure 5 Changes in myocardial oxygen consumption (MVO_2) and transmyocardial lactate extraction (lact extract) during phentolamine infusion Open bar = control values, hashed bar = values obtained during phentolamine infusion MVO_2 and transmyocardial lactate extraction did not change during phentolamine infusion

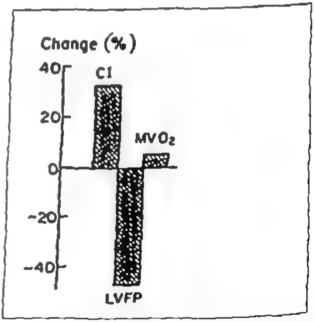

Figure 6 Relative changes in cardiac index (CI), left ventricular filling pressure (LVFP) and myocardial oxygen consumption (MVO_2) during phentolamine infusion Percentage changes from control are illustrated During phentolamine infusion cardiac index increased and left ventricular filling pressure decreased without any significant change in myocardial oxygen consumption

It needs to be emphasized that changes in global myocardial metabolic function may not reflect those of the ischemic myocardial segments. Without a knowledge of regional metabolism the possibility of increased hypoxia in some areas of the myocardium due to reduction of perfusion pressure during phentolamine therapy cannot be ruled out. Better knowledge of regional myocardial perfusion and metabolism will be most useful in determining the degree of reduction of arterial pressure that can be tolerated by individual patients. However, a significant reduction in arterial pressure, particularly in patients with AMI is likely to cause enhanced myocardial ischemia, despite a reduction in myocardial oxygen demand. It is imperative, therefore, that changes in arterial pressure be monitored during phentolamine therapy. In conclusion, phentolamine therapy produces a beneficial hemodynamic response in patients with AMI associated with pump failure and with elevated left ventricular filling pressure. In such patients global myocardial metabolism does not usually deteriorate. Improved mechanical performance of left ventricle is not usually associated with any increase in the metabolic cost. However, changes in regional myocardial metabolism and mechanical function during phentolamine infusion may be variable and unpredictable.

SUMMARY

Phentolamine, a potent vasodilator agent, improves left ventricular function in patients with left ventricular failure complicating AMI. In these patients a consistent increase in CO and a decrease in left ventricular filling pressure is observed. No significant change occurs in rate pressure product, coronary sinus flow, myocardial oxygen extraction and consumption, and in transmyocardial lactate extraction. Thus, improved left ventricular function with phentolamine in these patients is not associated with any increase in overall metabolic cost.

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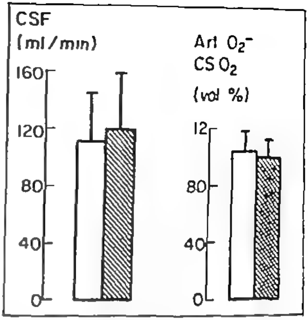

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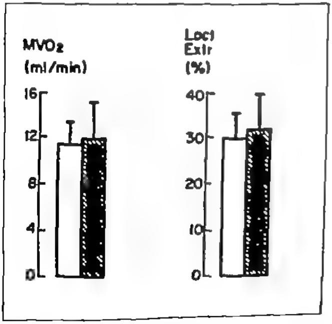

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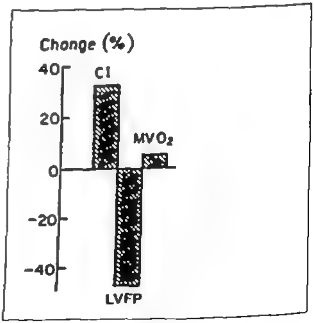

Figure 6 Relative changes in cardiac index (CI), left ventricular filling pressure (LVFP) and myocardial oxygen consumption (MVO_2) during phentolamine infusion Percentage changes from control are illustrated During phentolamine infusion cardiac index increased and left ventricular filling pressure decreased without any significant change in myocardial oxygen consumption

INFLUENCE OF NITROGLYCERIN ON CENTRAL HAEMODYNAMICS AND $\dot{V}_A/\dot{Q}_C$ OF THE LUNGS IN THE POSTOPERATIVE PERIOD AFTER CORONARY BYPASS SURGERY

Alf Holmgren, Elisabet Anjou, Lisbet Broman and Staffan Lundberg

Alveolar hypoxia causes vasoconstriction in the pulmonary vascular bed (Euler & Liljestrand 1946). This phenomenon is usually called hypoxic pulmonary vasoconstriction (HPV). HPV is a very potent mechanism which may completely abolish perfusion of a whole hypoxic lung if the hypoxia is chronic as in bronchial adenoma occluding but not blocking one main bronchus.

Induction of anaesthesia is followed by airway closure, formation of atelectasis (Marshall & Wyche Jr 1972), venous admixture and arterial hypoxemia. This hypoxemia is the result of perfusion of lung regions with low $\dot{V}_A/\dot{Q}$ and development of a right to left shunt ($\dot{Q}_{SH}$) through the lung. HPV is probably present in these hypoventilated regions. Administration of oxygen diminishes the effect of regional hypoventilation, increases tissue oxygen tension and oxygen tension of mixed venous blood and will therefore tend to release HPV partly or completely thereby increasing venous admixture. Furthermore breathing oxygen enriched air produces or increases shunt flow by causing absorption collapse of pulmonary units with low ventilation-perfusion ratios (Dantzker *et al.* 1975).

Administration of nitrates – sodium nitroprusside (SNP) or nitroglycerin (TNG) during cardiac, pulmonary, otolaryngologic operations and following vascular surgical procedures (Vettzer *et al.* 1976, Wildsmith *et al.* 1975) have resulted in a decreased arterial oxygen tension, increased right – left shunt and decreased pulmonary vascular resistance (PVR).

It has been suggested that these observations are compatible with the hypothesis that nitrates inhibit HPV.

The present study was undertaken to quantitate venous admixture in the postoperative period 21 h after operation, in patients undergoing elective coronary bypass surgery, to analyze the contribution of shunt and perfusion of regions with low V_A/Q to venous admixture, and to study the effect of constant infusion of nitroglycerin on $\dot{Q}_{SH}$ and $\dot{V}_A/\dot{Q}$.

To do this we have applied the inert gas technique developed by Wagner and co-workers 1974[a] which allows a description of the distribution of blood flow (Q) and ventilation (V) to 50 compartments with $\dot{V}_A/Q$ varied between 0.005 and 100.

PATIENTS

We investigated 10 patients. Nine men with a mean age of 55 years, SD±8, were without a history of a lung disease. 3 were smokers and 6 had stopped smoking at least 6 months before the investigation. One patient had asymptomatic asthma and will be reported separately.

All patients were undergoing elective bypass surgery for severe ischaemic heart disease (IHD).

ANAESTHESIA AND POSTOPERATIVE CARE

Ninety minutes after premedication with morphine, 10–15 mg, and scopolamine, 0.4–0.6 mg, according to age and weight anaesthesia was induced in 5 patients with diazepam, 10 mg, fentanyl, 0.1–0.2 mg and if necessary with thiopentone, 50–175 mg. Endotracheal intubation was performed under muscle relaxation with pancuronium bromide 0.1 mg kg^{-1} b.w.

Anaesthesia was maintained with small doses of fentanyl and nitrous oxide, 50 % in oxygen. In 4 patients anaesthesia was induced and maintained with high doses of fentanyl. The total dose during the operation amounted to 60–100 $\mu g \cdot kg^{-1}$ b.w. These patients were ventilated with oxygen, 50 % in air. Ventilation was controlled in all patients. During cardiopulmonary bypass the lungs were deflated and not ventilated or perfused. Anaesthesia was maintained with pen-

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DISCUSSION

Hörlyk
During how long time was the infusion maintained?

Chatterjee
The metabolic data and coronary sinus blood flow were measured at the time of the peak effect which was usually within 5–10 minutes after the optimum dose was administrated The infusion was maintained for 24–48 hours in individual patients, and then attempts were made to gradually decrease the infusion to see whether there was any hemodynamic and/or clinical deterioration. If there was no deterioration patients were maintained without phentolamine infusion However at least some of these patients needed long term vasodilator therapy

Hörlyk
I would also like to know the number of patients still alive after the investigation?

Chatterjee
In the group with normal filling pressures who received nitroprusside or phentolamine there was no in-hospital mortality Patients who had high left ventricular filling pressure were divided into two subsets: Those who had a stroke work index above 20 g m/m^2 and a wedge pressure above 15 mm Hg had a mortality of 9 % In another subset of patients who had a stroke work index less than 20 g m/m^2 but a filling pressure above 15 mm Hg with vasodilators had an in-hospital mortality about 40 % Three patients died from non-cardiac cause. If you eliminate these 3 patients the mortality was 32 % But in patients who had stroke work index less than 10 g m/m^2 and a high filling pressure, the mortality despite vasodilator therapy was about 87 %

RESULTS

Central haemodynamic variables. The haemodynamic results are presented in Figure 1 and Figure 2 and Table I. In the control situation the arterio-venous oxygen difference was slightly elevated 51 ml/l, indicating a slightly hypokinetic circulation. Heart rate was slightly elevated, 80 bpm, SD ± 11 and stroke volume within the normal range of variation. The SD was, however 17 ml indicating a wide variation.

Pulmonary arterial and wedge mean pressures were slightly low for the age. Pulmonary vascular resistance, right atrial mean pressure and the systemic arterial mean pressure were normal.

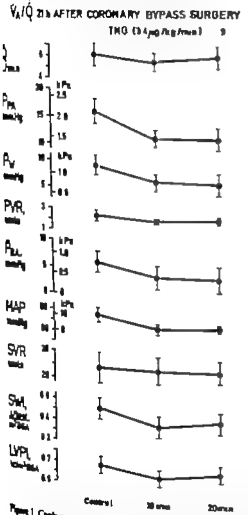

Figure 1 Cardiac output, Q l/min. Pulmonary arterial mean pressure P_{PA} mm Hg, pulmonary arterial wedge mean pressure P_W mm Hg, pulmonary vascular resistance, mm Hg/l/min/m²BSA, right atrial mean pressure, P_{RA} mm Hg, systemic arterial mean pressure, MAP mm Hg, systemic vascular resistance, mm Hg/l/min/m²BSA, left ventricular stroke work index, SWI, J/beat/m²BSA and left ventricular power index, W/m²BSA, before, control and after 10 and 20 min of constant infusion of nitroglycerin, TNG, mean 3.4 µg/kg/min in 9 patients 21 hours after coronary bypass surgery

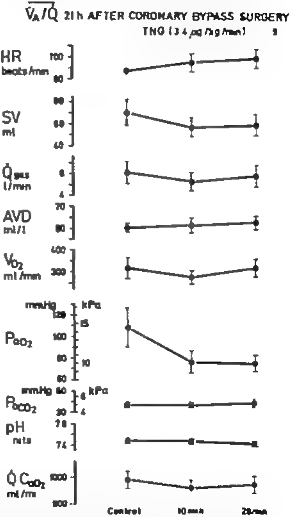

Figure 2 Heart rate, HR, bpm, stroke volume, SV ml cardiac output $\dot{Q}_{gas}$, l/min, weighted mean of $\dot{Q}$ determined with Fick principle for each of the six inert gases, arterio venous oxygen difference, AVD, ml/l, oxygen uptake, $\dot{V}_{O_2}$, ml STPD/min, arterial oxygen tension, P_aO_2, mm Hg, arterial carbon dioxide tension, P_aCO_2, mm Hg, pH, units and available oxygen, $\dot{Q}xCa_{O_2}$, ml/min before, control and after 10 and 20 min of constant infusion of nitroglycerin, TNG, mean 3.4 µg/kg/min in 9 patients, 21 hours after coronary bypass surgery

tobarbitone 5 mg kg^{-1} b w the purpose of which was also to protect the brain from accidental hypoxia during the bypass. After termination of the cardiopulmonary bypass mean perfusion time 138 min SD±45 min and throughout the postoperative course the patients were ventilated with an air-oxygen mixture adjusted to give blood gases within physiological range. Analgesia was achieved with morphine substituted by fentanyl 2–3 hours preceding the investigation. Diazepam was given when necessary. Fluid replacement consisted of 10 % glucose in water 600 ml m^2 BSA. Blood losses were substituted by whole blood plasma or 5 % albumin in glucose according to haemoglobin concentration hematocrit and clinical criteria like heart rate, peripheral temperature urine production and the relation between arterial pressures and filling pressures for the left and right heart. The fluid and blood balance at the time of the investigation calculated from the onset of the operation was 1370 ml SD±910 and 1060 ml SD ±660 respectively.

METHODS AND PROCEDURE

The patients were studied in the morning on the day after operation. Ventilation was controlled (Engström 300 LKB Medical Sweden) and adjusted to maintain a normal arterial P_{CO_2}. Zero endexpiratory pressure was used and the rate of breathing was 20 cpm. F_{IO_2} averaged 0 40 SD±0 04.

In connection with the induction of anaesthesia catheters had been introduced into the pulmonary artery superior vena cava left radial artery and a peripheral vein. ECG and pulmonary right atrial pulmonary wedge or left atrial pressures were monitored during the whole procedure.

The measurements of the distribution of $\dot{V}/\dot{Q}$ ratios were performed according to the technique reported by Wagner and co-workers 1974 using a constant infusion of a mixture of 6 inert gases (SF_6 ethane cyclopropane halothane ether and acetone) dissolved in tracer concentrations in saline through a peripheral intravenous catheter at a rate of 2.9 ml/min. Measurements started following 30 min infusion of the saline containing the inert gases. Blood samples were withdrawn for determination of blood gas contents, pressures, P_{50} and buffer line of the mixed venous blood. The 7.5 ml blood samples were withdrawn into a 50 ml matched barrel glass syringe. Mixed expired gas was withdrawn with 20 ml Hamilton gas tight syringe heated to 55°C in a heating box, after passing through a heated (55°C) mixing box and a heated (55°C) valve system that parted inspired from expired air close to the mouth end of the endotracheal tube. The delay for withdrawal of gas samples in relation to that of the blood samples was determined by dividing the volume of the mixing box with the observed ventilation. The gas syringes were stored at 55°C until analyzed to avoid condensation of water vapour which would trap the acetone in the gas sample.

Inert gas concentrations were determined with a Perkin Elmer F_{42} head space analyzer equipped with FID and ECD a single column and splitter. The 1 5 m column was packed with Porapax QS, 50/80 mesh. Oven temperature 130°C ECD temperature 250°C and FID temperature 250°C. Carrier gas flow 15 ml nitrogen/min.

The expired air was also analyzed for O_2 CO_2 and N_2 with a Centronics masspectrometer. Oxygen content of blood samples was determined with an Instrumentation Laboratories CO-oximeter 282. Gas tensions and pH were determined with an IL Micro Autocal pH/blood gas Analyzer 613. The oxygen contents were corrected for dissolved oxygen. P_{50} was determined according to Aberman *et al* (1975). The blood buffer line was established with the microequilibration technique of Siggaard Andersen *et al* (1960).

Blood samples for blood gas determination were anticoagulated with heparin and stored in ice water until analyzed usually within 20 min. Blood samples for spectrophotometry were anticoagulated with EDTA.

After control measurements an i v infusion of TNG was started at a mean rate of 3 4 µg kg^{-1} (range 0 75–9 5) with the aim to lower radial arterial mean pressure to 65 mm Hg. The infusion of inert gases was continued at the same rate as before and measurements of pressures, flow alveolar gas exchange blood gases and the distribution of $\dot{V}_A/\dot{Q}$ were repeated after 10 min and 20 min infusion of TNG. Current statistical methods were used and paired differences were analyzed with students t test.

RESULTS

Central haemodynamics. The haemodynamic results are presented in Figure 1 and Figure 2 and Table I.

In the control situation the arterio-venous oxygen difference was slightly elevated 51 ml/l indicating a slightly hypokinetic circulation. Heart rate was slightly elevated, 80 bpm, SD±11 and stroke volume within the normal range of variation. The SD was, however 17 ml indicating a wide variation.

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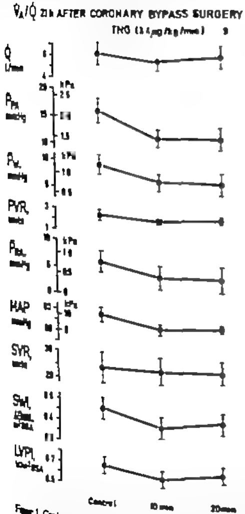

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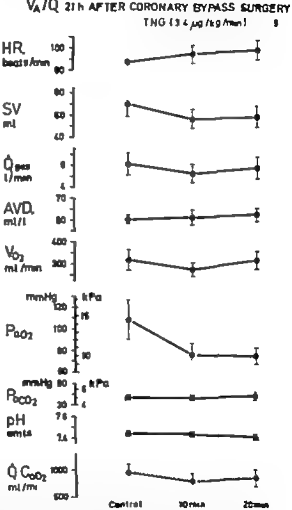

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The arterial oxygen tension was normal 108 mm Hg but the alveolo-arterial partial pressure difference increased 144 mm Hg. The total venous admixture (Q_{VA}/Q_T) averaged 11.3 per cent. Arterial P_{CO_2} and acid base status were normal.

The retention and excretion curves for the inert gases indicate the presence of a shunt of 6.4 per cent and a total dead space (V_D/V_T) including apparatus dead space of 0.22. The mean $V_A/\dot{Q}$ for the blood flow distribution was 0.88 with a mean value for the log SD of ±1.14. The mean $V_A/\dot{Q}$ for the ventilation distribution was 1.16 and the mean for log SD ±0.64. This indicated the presence of increased V_A/Q inequality compared to what has been observed in healthy volunteers of the same age as the present patients (Wagner *et al.* 1974b). There was also a small mode of perfusion in the V_A/Q ranges 0–0.01 and 0.01–0.1 which explains the difference between $\dot{Q}_{VA}/\dot{Q}_T$ and $\dot{Q}_{SH}/\dot{Q}_T$.

Constant infusion of TNG resulted in a planned decrease of arterial mean blood pressure to a level of 65 mm Hg with SD of ±7 mm Hg. Cardiac output decreased almost significantly after 10 min from 6.1 to 5.3 litres/min and then increased again to 5.8 l/min after 20 min infusion. Heart rate increased 10 bpm ($p<0.001$) and stroke volume decreased. The filling pressures for the right and left heart were slightly decreased. Pulmonary vascular resistance was slightly reduced while systemic vascular resistance was unchanged.

Table I. Fraction of oxygen in inspired air FI_{O_2}, cardiac output $\dot{Q}$ gas, l min^{-1} determined as the weighted means of Q calculated for each inert gas using Fick's principle, arterio venous oxygen difference AVD ml l^{-1}, heart rate, HR, bpm, stroke volume, SV ml, total ventilation VE, l BTPS min^{-1}, oxygen uptake, $\dot{V}_{O_2}$ ml STPD·min^{-1}, pulmonary arterial mean pressure, $\bar{P}_{PA}$ mm Hg, pulmonary arterial wedge pressure $\bar{P}_W$ mm Hg, pulmonary vascular resistance PVR mm Hg·l^{-1} min m^{2}BSA units, right atrial mean pressure $\bar{P}_{RA}$ mm Hg, radial arterial mean pressure, MAP mm Hg, systemic vascular resistance, SVR mm Hg·l^{-1} min m^{2}BSA, units, arterial oxygen tension, P_{aO_2} mm Hg and arterial carbon dioxide tension, P_{aCO_2} mm Hg, venous admixture $\dot{Q}_{VA}/\dot{Q}_T$, relative shunt flow $\dot{Q}_{SH}/\dot{Q}_T$ and mixed (m) and ideal (i) alveolar arterial oxygen pressure differences, D_{A-a} mm Hg in 9 patients, 21 hours after coronary bypass surgery before, control, and after 10 and 20 min of constant infusion of TNG mean 3.4 µg/kg^{-1} min^{-1}. Significance of differences between observations after 10 or 20 min and control are indicated with * = almost significant ($p\leq0.05$), ** = significant ($p\leq0.01$), *** = highly significant ($p<0.001$).

Variable	Units	Control	±SD	10' after	±SD	20' after	±SD
FI_{O_2}		0.40	±0.04	0.40	±0.04	0.40	±0.04
$\dot{Q}_{GAS}$	l min^{-1}	6.1	±1.5	5.3	±1.3	5.8	±1.5
AVD	ml·l^{-1}	51	±6	53	±10	56	±9
HR	bpm	88	±11	94**	±12	98***	±13
SV	ml	70	±17	57	±13	99	±14
$\dot{V}_E$	l BTPS·min^{-1}	8.7	±0.8	9.0	±0.5	9.1	±0.7
$\dot{V}_{O_2}$	ml STPD·min^{-1}	317	±71	275	±45	319	±64
$\bar{P}_{PA}$	mm Hg	16	±3	11**	±2	11**	±3
$\bar{P}_W$	mm Hg	9	±3	6	±2	6**	±3
PVR	units	2.4	±0.7	1.9*	±0.3	2.0	±0.4
$\bar{P}_{RA}$	mm Hg	[illegible]	±3	3**	±3	3 **	±4
MAP	mm Hg	76	±10	64	±7	65	±5
SVR	units	24	±9	24	±7	23	±7
P_aO_2	mm Hg	108	±26	76***	±17	75	±12
P_aCO_2	mm Hg	37	±3	37	±3	39	±5
$\dot{Q}_{VA}/\dot{Q}_T$		11.3	±3.6	16.9*	±4.5	16.5	±3.8
$\dot{Q}_{SH}/\dot{Q}_T$		6.4	±4.5	12.2**	±6.3	12.8**	±4.0
D_{A-a} (m)	mm Hg	144	±29	178**	±28	178 **	±33
D_{A-a} (i)	mm Hg	132	±28	166	±28	162*	±30

There was a marked decrease in P_{aO_2} from 108 mm Hg to 76 and 75 mm Hg respectively.

The retention and excretion curves for the inert gases showed an increase of the shunt to an average of 12.2 and 12.8 per cent of cardiac output while $\dot{Q}_{VA}/\dot{Q}_T$ increased to 16.9 and 16.5 per cent.

The mean $\dot{V}_A/\dot{Q}$ for the Q and V distribution was slightly increased but not significantly so. The mean for the ventilation distribution behaved in a similar manner. The perfusion and ventilation of the small mode with low $\dot{V}/\dot{Q}$ observed in the control situation remained unchanged. This is also illustrated in Figure

$\overline{\dot{V}_A/\dot{Q}}$ 21 h AFTER CORONARY BYPASS SURGERY EFFECT OF TNG 14 μg/kg/min

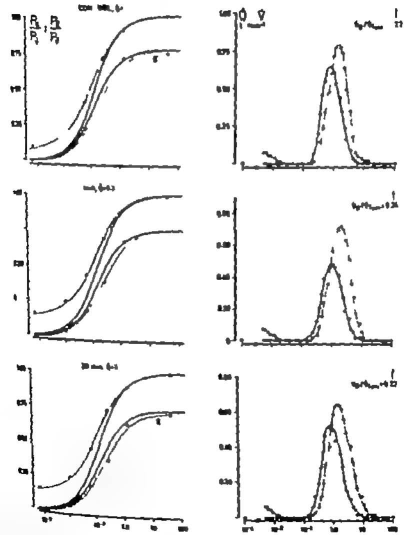

Figure 3. Mean retention – solubility, R, and excretion-solubility, E, curves, left, obtained from 9 patients 21 hours after coronary bypass surgery before, control and after 10 and 20 min of constant infusion of nitroglycerin, TNG, mean 14 μg/kg/min. Associated representative distributions of $\dot{V}_A/\dot{Q}$ ratios on the right. These mean curves were obtained as the arithmetic mean of relative perfusion, ($\dot{Q}/\dot{Q}_T$) and relative ventilation ($\dot{V}/\dot{V}_T$), for each of 50 compartments and therefore implies some smoothing of the original curves.

The arterial oxygen tension was normal 108 mm Hg but the alveolo-arterial partial pressure difference increased 144 mm Hg. The total venous admixture (Q_{VA}/Q_T) averaged 11.3 per cent. Arterial P_{CO_2} and acid base status were normal.

The retention and excretion curves for the inert gases indicate the presence of a shunt of 6.4 per cent and a total dead space (V_D/V_T) including apparatus dead space of 0.22. The mean $V_A/\dot{Q}$ for the blood flow distribution was 0.88 with a mean value for the log SD of ± 1.14. The mean $V_A/\dot{Q}$ for the ventilation distribution was 1.16 and the mean for log SD ± 0.64. This indicated the presence of increased V_A/Q inequality compared to what has been observed in healthy volonteers of the same age as the present patients (Wagner *et al* 1974b). There was also a small mode of perfusion in the $V_A/\dot{Q}$ ranges 0–0.01 and 0.01–0.1 which explains the difference between $\dot{Q}_{VA}/\dot{Q}_T$ and $\dot{Q}_{SH}/\dot{Q}_T$.

Constant infusion of TNG resulted in a planned decrease of arterial mean blood pressure to a level of 65 mm Hg with SD of ± 7 mm Hg. Cardiac output decreased almost significantly after 10 min from 6.1 to 5.3 litres/min and then increased again to 5.8 l/min after 20 min infusion. Heart rate increased 10 bpm ($p<0.001$) and stroke volume decreased. The filling pressures for the right and left heart were slightly decreased. Pulmonary vascular resistance was slightly reduced while systemic vascular resistance was unchanged.

Table I. Fraction of oxygen in inspired air F_{IO_2}, cardiac output, $\dot{Q}$ gas, l min^{-1} determined as the weighted means of $\dot{Q}$ calculated for each inert gas using Fick's principle, arterio venous oxygen difference, AVD ml l^{-1}, heart rate HR bpm, stroke volume, SV ml, total ventilation $\dot{V}_E$, l BTPS min^{-1}, oxygen uptake, V_{O_2} ml STPD·min^{-1}, pulmonary arterial mean pressure, $\bar{P}_{PA}$ mm Hg, pulmonary arterial wedge pressure, $\bar{P}_W$ mm Hg, pulmonary vascular resistance, PVR mm Hg l^{-1} m^{2}BSA, units, right atrial mean pressure, $\bar{P}_{RA}$ mm Hg, radial arterial mean pressure MAP mm Hg, systemic vascular resistance, SVR, mm Hg l^{-1} min· m^{2}BSA units, arterial oxygen tension, P_{aO_2} mm Hg and arterial carbon dioxide tension, P_{aCO_2}, mm Hg, venous admixture $\dot{Q}_{VA}/\dot{Q}_T$ relative shunt flow $\dot{Q}_{SH}/\dot{Q}_T$ and mixed (m) and ideal (i) alveolar arterial oxygen pressure differences, D_{A-a} mm Hg in 9 patients, 21 hours after coronary bypass surgery before, control, and after 10 and 20 min of constant infusion of TNG mean 3.4 µg/kg^{-1} min^{-1}. Significance of differences between observations after 10 or 20 min and control are indicated with * = almost significant ($p\leq 0.05$), ** = significant ($p\leq 0.01$), *** = highly significant ($p<0.001$)

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CONCLUDING REMARKS

The patients in this study had given their informed consent to the investigations. All catheters were introduced as part of the standard routine at this unit.

Before operation patients with coronary artery disease can be expected to have a blood volume about 20 per cent less than predicted from body weight (Åborn *et al.* 1979). The i.v. anaesthetic agents used during the operation and in the postoperative period do not seem to influence HPV (Bjaertnaes 1977). In 5 patients nitrous oxide was used in connection with the surgical procedure at least 22 hours before the study. The perfusion times were of standard length. None had undergone reoperation for haemorrhage at the time of investigation. Blood and fluid balance were positive. The patients were slightly hypokinetic and had small stroke volumes and moderate tachycardia. They had a moderate systemic hypotension and the pulmonary arterial, right and left ventricular filling pressures were slightly low. We have regarded the patients as having a slight relative hypovolemia.

In the control period the mean $\dot{V}_A/\dot{Q}$ of the perfusion distribution was higher than earlier reported for healthy old subjects, (39–60 years) (Wagner *et al.* 1974) and anaesthetized patients with obstructive lung disease (Dueck *et al.* 1980). The same holds true for mean $\dot{V}_A/\dot{Q}$ of the ventilation distribution. Log standard deviation is large for both distributions and of the same order as earlier reported by Dueck *et al.* 1980 although no anaesthetic gas was used in the present study at the time of measurement.

The presence of a marked shunt in these patients is compatible with partial release of HPV probably due to the elevated inspired oxygen tension which increase mixed venous oxygen tension as well as the oxygen tension of ventilated areas of the lung. The anatomic basis for this shunt is probably vessels located to atelectatic areas.

Administration of nitroglycerin seems to have a selective effect on these HPV vessels with only minor changes in the main distribution of perfusion in relation to $\dot{V}_A/\dot{Q}$. There was an almost significant shift in the mean of the ventilation distribution towards regions with higher $\dot{V}_A/\dot{Q}$. This change probably relates to the decrease in pulmonary blood volume which can be expected following TNG relaxation of the systemic capacitance vessels. These results are in agreement with those reported by Colley *et al.* 1979 who studied the effect of nitroprusside on HPV in normal and edematous dog lungs and who also demonstrated a partial or total abolition of HPV and/or formation of new absorption atelectasis during breathing of 100

Table II. Relative perfusion, $\dot{Q}/\dot{Q}_T$ per cent, and relative ventilation $\dot{V}/\dot{V}_E$, per cent, of seven different ranges of $\dot{V}_A/\dot{Q}$ in a 50 compartment lung model (upper part) and mean $\dot{V}_A/\dot{Q}$ for the distributions of perfusion and ventilation with mean values for the log standard deviation of these distributions (lower part). Results before control and after 10 and 20 min of constant infusion of TNG mean 3.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in 9 patients 21 hours after coronary bypass surgery are presented.

$\dot{V}_A/\dot{Q}$-range	$\dot{Q}/\dot{Q}_T \cdot 100$			$\dot{V}/\dot{V}_E \cdot 100$		
	Control	10'	20'	Control	10'	20'
0	6.4	12.2	12.8	0	0	0
0–0.05	3.3	3.2	2.4	0	0	0
0.05–0.1	1.8	1.7	1.1	0	0	0
0.1–1.0	45.4	35.2	42.6	22.2	15.2	18.3
1.0–10	43.1	47.6	40.9	55.2	59.8	53.1
10–100	0.1	0.1	0.3	0.6	0.6	1.8
100–	0	0	0	22.0	24.3	26.7
$\dot{V}_A/\dot{Q}$	0.88	1.02	0.95	1.61	2.03	1.92
±Log SD	1.14	1.24	1.10	0.64	0.69	0.78

4 where $\dot{Q}/Q_T$ and V/V_T the distributions of relative blood flow and relative ventilation for all three measurements have been plotted in the same diagram All patients showed an increase in $\dot{Q}_{SH}/\dot{Q}_T$ with only minor changes in the mean Q and V distributions.

Perfusion and ventilation of regions with high V_A/Q were observed in 4/9 patients as could be expected if blood was shifted from the pulmonary vascular bed to the systemic circulation due to a relaxation of the systemic capacitance vessels

One patient had asthma and is reported separately In the control state this patient had the lowest observed $Q_{SH}/\dot{Q}_T$ 0 8 per cent The circulation was hypokinetic with a slight arterial hypotension. The p had tachycardia, 90 bpm and the stroke volum low The inspired oxygen fraction was 0.29 an A-a oxygen pressure difference was 97 mm Hg mean of the Q distribution was 1 11 with a k of 0 92 There was an increase in the amount of tilation going to areas with high $V_A/\dot{Q}$ $\dot{Q}_{V/}$ amounted to 4 4 per cent

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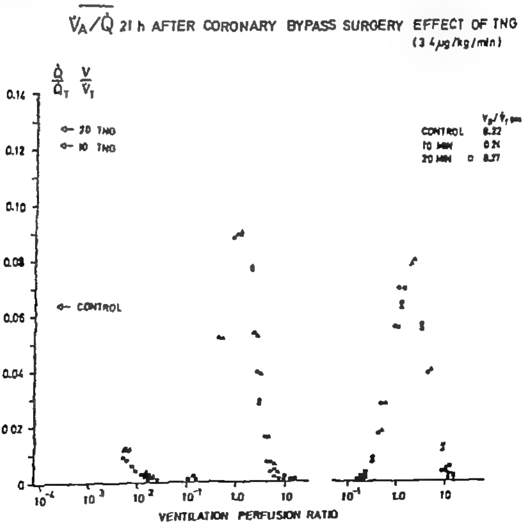

Figure 4 Relative perfusion, $\dot{Q}/\dot{Q}_T$ to the left and ventilation, $\dot{V}/V_T$ to the right in relation to $\dot{V}_A/\dot{Q}$ in a 50 compartment model, before, control filled circles and after 10 min, filled triangles and 20 min filled squares of constant infusion of nitroglycerin, TNG mean 3 4 µg/kg/min Note the changes in shunt while the main mode of distribution as well a mode including perfusion of areas with low $V_A/\dot{Q}$ re unchanged Fractional dead space ventilation, $\dot{V}_D/\dot{V}_T$ termined with the inert gas technique increases sligh

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0.01–0.1	1.8	1.7	1.1	0	0	0
0.1–1.0	45.4	35.2	42.6	22.2	15.2	18.3
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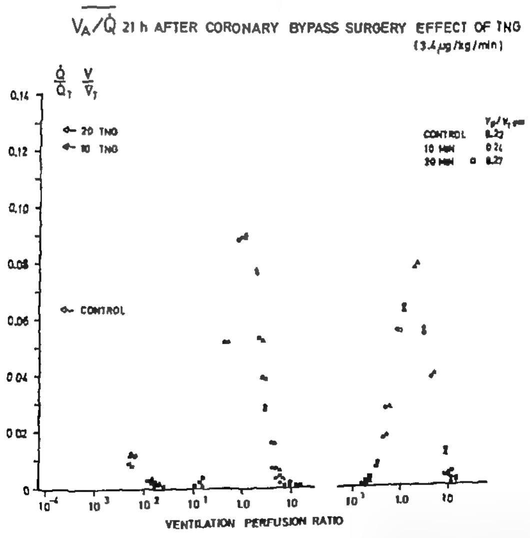

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per cent oxygen (Colley *et al* 1979 Dantzker *et al* 1975)

Almost identical observations were made in this laboratory in a similar patient group using identical procedures techniques under infusion of prenalterol – a positive inotropic agent which increased cardiac output by 2 l/min with unchanged pressures Also in this situation were the changes located to a similar group of vessels – probably under partially released HPV with an increase in $Q_{SH}/\dot{Q}_T$ of the same order as after administration of nitroglycerin It is of interest to note that the patient with asthma had the smallest observed $\dot{Q}_{SH}/\dot{Q}_T$ in the present study The rest of the distribution had a bimodal configuration both for perfusion and ventilation The same configuration has earlier been reported in patients with obstructed lung diseases type II (Wagner *et al* 1977) The shunt in this patient reacted to TNG in a similar manner as in the rest of the patients but with a smaller magnitude. Nitroglycerin also increased the mode with high V_A/Q more than observed in the rest of the patients probably due to a decrease in pulmonary blood volume. The explanation for the small shunt in this patient could be that the hyperinflated lungs had a lesser tendency to collapse of the small airways in connection with the general anaesthesia and/or lower tissue oxygen tensions due to regional hypoventilation

SUMMARY

We investigated 9 patients with normal lungs all men and one female patient with asthma, 21 hours after bypass surgery before and after 10 and 20 min infusion of nitroglycerin, TNG mean 3 4 $\mu g\ kg^{-1}\ min^{-1}$ to lower the systemic arterial mean blood pressure to about 65 mm Hg. The patients were all intubated and ventilated with a respirator and in a diazepam – fentanyl anaesthesia. Pressures were measured in the pulmonary artery and wedge right atrium and radial artery

A continuous distribution of perfusion and ventilation in relation to $V_A/\dot{Q}$ was established with the inert gas technique of Wagner and co-workers

In the control situation all patients were slightly hypokinetic with slightly low pulmonary and systemic arterial right and left filling pressure of the heart.

There was a mean Q_{SH}/Q_T of 6 4 per cent and a V_D/V_T of 0 22. Mean $\dot{Q}$-distribution was 1 02 with a mean log SD$\pm$1 14 and mean V-distribution of 1.61 with a mean log SD$\pm$0 64 indicating inhomogenity in V_a/Q of the lungs.

Infusion of TNG resulted in a slight reduction of cardiac output a significant increase in heart rate and decrease in stroke volume. Arterial P_{O_2} fell significantly while P_{CO_2} and pH did not change. Radial and pulmonary arterial mean pressure, right and left ventricular filling pressure were reduced significantly

The decrease in arterial oxygen tension was mainly due to an increased shunt flow probably due to a release of hypoxic vasoconstriction. The rest of the perfusion and ventilation distributions remained unchanged Only four per cent of venous admixture, Q_{VA}/Q_T after administration of TNG was due to perfusion of hypoventilated regions.

The reduction of the pressures in the pulmonary vascular bed was accompanied by an increased ventilation of areas with high V_A/Q

The patient with asthma had the lowest observed shunt but behaved otherwise in a similar manner as the patients without lung disease

(References see next page)

HAEMODYNAMIC EFFECTS OF PRAZOSIN IN CHF

Stuart R. Reuben, Peilong Kuan, Elsie J. Gale and Pamela M. Wilde

INTRODUCTION

During the last decade there has been considerable interest in the use of systemic vasodilator drugs in the management of acute and chronic heart failure (CHF). Majid and co-workers (1971) showed that infusions of phentolamine produced considerable benefit in severe left ventricular failure following acute myocardial infarction (AMI), while Franciosa *et al* 1972 demonstrated similar haemodynamic benefit with sodium nitroprusside infusions. More recently attention has focused on the use of vasodilator therapy in the management of chronic, resistant CHF and haemodynamic improvement has been shown with oral nitrates (Franciosa *et al* 1974) and hydralazine (Chatterjee *et al* 1976). The therapeutic use of vasodilators in CHF has been critically examined by Chatterjee & Parmley 1977 and these workers present a strong theoretical basis for such an approach.

We were interested to evaluate the acute haemodynamic effects of the post-synaptic alpha adrenoceptor blocking drug, prazosin, in severe CHF resistant to conventional therapy with digitalis and diuretics. Furthermore, we were interested to see if tolerance to the drug developed by measuring cardiac output (CO) serially during chronic treatment.

PATIENTS AND METHODS

Eleven patients with chronic CHF due to advanced coronary artery disease (6 patients) or congestive cardiomyopathy (5 patients), were investigated by cardiac catheterization. All patients were receiving therapy with digoxin and high doses of frusemide and these were continued throughout the study period in unchanged doses. The nature and purpose of the study was carefully explained and all patients gave written consent and the protocol was approved by the hospital ethics committee.

At cardiac catheterization, simultaneous measurements were made of aortic, left ventricular, pulmonary artery and right atrial pressures. Cardiac output was measured by the indocyanine green dye-dilution technique with pulmonary artery injection of dye and aortic sampling through a Waters cuvette-densitometer. Paired estimates were performed and were analysed by semi-logarithmic replotting of the decay slope. The paired estimates agreed within 5 %.

Systemic vascular resistance (SVR) was calculated as:

$$SVR = (Ao - RA) \times 80/Q \text{ dynes sec cm}^{-5}$$

where Ao = mean aortic pressure (mm Hg)
RA = mean right atrial pressure (mm Hg)
and Q = cardiac output (L/min)

Left ventricular stroke work index (LVSWI) was calculated as

$$LVSWI = (Ao - LVEDP) \times SI \times 0.0136 \text{ g-m/m}^2$$

where Ao = mean aortic pressure (mm Hg)
LVEDP = left ventricular end-diastolic pressure (mm Hg)
and SI = stroke index (ml/beat/m^2)

The haemodynamic measurements were determined in all patients at rest, before and 60 minutes after an oral dose of prazosin 3.5 mg. Statistical analysis was performed using the Student's t-test for paired data.

After the acute haemodynamic study the patients received chronic prazosin therapy in a dose of one mg 3 times a day. We measured CO by the single breath nitrous oxide whole body plethysmograph method prior to catheterization and 1, 2, 3 and 4 and 8 weeks after the start of chronic therapy. The nitrous oxide whole body plethysmograph method for the

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HAEMODYNAMIC EFFECTS OF PRAZOSIN IN CHF

Stuart R Reuben, Peilang Kuan Elsie V Gale and Pamela M Wilde

INTRODUCTION

During the last decade there has been considerable interest in the use of systemic vasodilator drugs in the management of acute and chronic heart failure (CHF) Majid and co-workers (1971) showed that infusions of phentolamine produced considerable benefit in severe left ventricular failure following acute myocardial infarction (AMI), while Franciosa *et al* 1972 demonstrated similar haemodynamic benefit with sodium nitroprusside infusions More recently attention has focused on the use of vasodilator therapy in the management of chronic, resistant CHF and haemodynamic improvement has been shown with oral nitrates (Franciosa *et al* 1974) and hydralazine (Chatterjee *et al* 1976) The therapeutic use of vasodilators in CHF has been critically examined by Chatterjee & Parmley 1977 and these workers present a strong theoretical basis for such an approach

We were interested to evaluate the acute haemodynamic effects of the post-synaptic alpha adrenoceptor blocking drug, prazosin, in severe CHF resistant to conventional therapy with digitalis and diuretics Furthermore, we were interested to see if tolerance to the drug developed by measuring cardiac output (CO) serially during chronic treatment

PATIENTS AND METHODS

Eleven patients with chronic CHF due to advanced coronary artery disease (6 patients) or congestive cardiomyopathy (5 patients), were investigated by cardiac catheterization All patients were receiving therapy with digoxin and high doses of frusemide and these were continued throughout the study period in unchanged doses The nature and purpose of the study was carefully explained and all patients gave written consent and the protocol was approved by the hospital ethics committee

At cardiac catheterization, simultaneous measurements were made of aortic left ventricular pulmonary artery and right atrial pressures Cardiac output was measured by the indocyanine green dye-dilution technique with pulmonary artery injection of dye and aortic sampling through a Waters cuvette-densitometer Paired estimates were performed and were analysed by semi-logarithmic replotting of the decay slope. The paired estimates agreed within 5 %

Systemic vascular resistance (SVR) was calculated as:

SVR = (Ao–RA) x 80/Q dynes sec cm^{-5}
where Ao = mean aortic pressure (mm Hg)
RA = mean right atrial pressure (mm Hg)
and Q = cardiac output (L/min)

Left ventricular stroke work index (LVSWI) was calculated as

LVSWI = (Ao LVEDP) x SI x 0 0136 g–m/m^2
where Ao = mean aortic pressure (mm Hg)
LVEDP = left ventricular end-diastolic pressure (mm Hg)
and SI = stroke index (ml/beat/m^2)

The haemodynamic measurements were determined in all patients at rest, before and 90 minutes after an oral dose of prazosin 3 5 mg. Statistical analysis was performed using the Student's t-test for paired data.

After the acute haemodynamic study the patients received chronic prazosin therapy in a dose of one mg 3 times a day We measured CO by the single breath nitrous oxide whole body plethysmograph method prior to catheterization and 1 2, 3 and 4 and 8 weeks after the start of chronic therapy The nitrous oxide whole body plethysmograph method for the

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measurement of pulmonary capillary blood flow and right ventricular stroke volume has been described in detail by Bosman and co-workers 1964 and Karatzas & Lee 1970 This method has been shown to be simple, reliable and reproducible and good correlations have been found with the Fick principle (Bosman *et al* 1964) and dye-dilution techniques (Reuben 1970).

We used a modified Vickers Medical Research hyperbaric oxygen chamber as the body plethysmograph and incorporated a pneumatic transducer as described by Karatzas *et al* 1969

RESULTS

Table I summarizes the group mean values for the haemodynamic variables and it can be seen that there is no significant change in heart rate following prazosin The mean left ventricular end-diastolic pressure was 29 mm Hg and this decreased by 37 9 % ($p<0\ 001$) after prazosin. This striking fall in left ventricular end diastolic pressure was accompanied by an 18 2 % increase in cardiac index ($p<0\ 01$) and a 23.5 % increase in left ventricular stroke work index ($p<0\ 01$) Mean pulmonary artery pressure decreased by 28 6 % ($p<0\ 01$) from 35 mm Hg to 25 mm Hg while mean aortic pressure declined by only 12.2 % ($p<0\ 05$). Systemic vascular resistance was reduced significantly by 19.3 % ($p<0\ 01$) from 1849 dyne sec. cm^{-5} to 1492 dyne. sec cm^{-5} There was a nonsignificant fall in mean right atrial pressure from 9 mm Hg to 6 mm Hg.

Table II shows the group mean cardiac indices fo the serial measurements during the 8 week study period. The pre-acute haemodynamic study value is significantly lower than the control value at catheterization. This difference is probably due to the increased sympathetic drive from the anxiety of undergoing a detailed haemodynamic study

After 2 weeks chronic therapy there was a highly significant increase in cardiac index from 1 7 $L/min/m^2$ to 3 10 $L/min/m^2$ ($p<0\ 001$). This increase in cardiac index was maintained over the next 6 weeks and amounted to an 82 % improvement.

CONCLUSIONS

Chronic CHF may manifest itself as pulmonary congestion leading to dyspnoea either on exertion or at rest (backward failure) or poor tissue perfusion resulting in fatigue and deteriorating renal function (forward failure). These usually co-exist but one may dominate and be refractory to conventional therapy with digoxin and high doses of diuretics. Systemic vasodilator drugs may act either on the arteriolar or venular beds, or both The observed haemodynamic response will depend very much on the degree of arteriolar or venodilatation produced by the drug. Franciosa *et al* 1974 has shown that oral long-acting nitrates act predominantly on the venous bed with considerable reduction of left ventricular end-diastolic pressure and relief of pulmonary congestive symptoms. Chatterjee *et al* (1976) has shown that hydralazine acts predominantly

Table I. Mean (± SE of mean) values of haemodynamic variables before and 60 minutes after oral prazosin in patients with chronic CHF (N = 11).

	Control	60 minutes post prazosin	
Heart rate (beats/min)	80±7 6	78±7 3	
Left ventricular end-diastolic pressure (mm Hg)	29±2 1	18±1 9	($p<0\ 001$)
Mean aortic pressure (mm Hg)	90±3.9	79±3 5	($p<0\ 05$)
Mean pulmonary artery pressure (mm Hg)	35±4 0	25±3 9	($p<0\ 01$)
Mean right atrial pressure (mm Hg)	9±4 5	6±3 6	
Cardiac index ($l/min/m^2$)	2 11±0.18	2 58±0.21	($p<0\ 01$)
Systemic vascular resistance (dyne. sec. cm^{-5})	1849±184	1492±158	($p<0\ 01$)
Left ventricular stroke work index ($gm.m/m^2$)	23.8±3.5	29 4±3 7	($p<0\ 01$)

Table II Mean (± SE of mean) values of cardiac index measured serially

Control	1 Week	2 Weeks	3 Weeks	4 Weeks	8 Weeks
1.75±0.11	2.08±0.18	3.10±0.20 $p<0.001$	2.65±0.19 $p<0.01$	3.05±0.23 $p<0.001$	3.10±0.21 $p<0.001$

on the arteriolar bed with increases in CO and stroke work but little effect on the elevated left ventricular end-diastolic pressure.

In the present study we have demonstrated that prazosin has a potent effect on both the venous and arteriolar beds, producing significant falls in left ventricular end-diastolic pressure, pulmonary artery pressure, aortic pressure and systemic vascular resistance with increases in cardiac index and stroke work index. All patients showed these responses but the magnitude of change was greatest in those patients with the highest initial left ventricular end-diastolic pressure.

All the patients experienced subjective improvement in effort dyspnoea during chronic therapy and this was matched by the highly significant increases in cardiac index found in the serial non-invasive studies (Table II)

There have been suggestions that tolerance to systemic vasodilators can develop in patients with CHF (Arnold et al 1978) We suggest that our serial measurements of cardiac index by the nitrous oxide whole body plethysmography method are evidence that tolerance in such patients does not occur during chronic prazosin therapy Moreover there was no significant change in body weight in our patients nor was there any need to increase the dose of diuretic therapy during the study period

Twelve months after the acute haemodynamic study 5 patients had improved sufficiently to return to a normal working life. Three patients improved symptomatically but not sufficiently to resume their previous employment, while 3 patients with coronary artery disease died of a further myocardial infarction

Prazosin would appear to combine the benefits of hydralazine and the long-acting nitrates and would seem to be valuable in patients with CHF resistant to conventional therapy The greatest value would appear to be in those patients with predominant pulmonary congestive symptoms who are not responding to large doses of diuretics The role of prazosin may be to alleviate pulmonary congestive symptoms without the problems of increasing renal dysfunction and rising blood urea, which too often complicates high dose diuretic therapy

SUMMARY

The acute haemodynamic effects of oral prazosin have been studied, at cardiac catheterization, in 11 patients with CHF In all patients there was a significant fall in left ventricular end-diastolic pressure, mean aortic and pulmonary artery pressure and systemic vascular resistance 60 minutes after 3.5 mg of prazosin There was no significant change in heart rate but there was a significant increase in cardiac index and left ventricular stroke work index The patients received chronic therapy with prazosin one mg 3 times a day and CO was measured serially by the nitrous oxide whole body plethysmograph method There was a sustained increase in cardiac index of [illegible] % during the 8 week study period Twelve months after the initial haemodynamic study 5 patients had improved sufficiently to return to normal work A further 3 patients were improved symptomatically but were unable to return to their previous employment. Three patients died of a myocardial infarction Prazosin has proved to be beneficial in CHF resistant to digitalis and diuretics

Acknowledgements

We are indebted to Mrs Anne Lake for her considerable help in the organisation of the study and in preparation of the manuscript

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LOSS OF PRAZOSIN EFFECT IN SEVERE CHRONIC CHF

Halfdan Ihlen, Erik Thaulow, John Kjekshus and Kolbjørn Forfang

Reports on the effects of prazosin in chronic congestive heart failure (CHF) are conflicting (Aronow *et al.* 1979, Awan *et al.* 1977, Colucci *et al.* 1980, Packer *et al.* 1979, Rubin *et al.* 1979). Few reports on the long term effects of prazosin have been presented. The aim of this study was to measure invasively the hemodynamics during the first hours of bed rest, during the first three days of prazosin treatment, and then after 6 weeks of treatment.

MATERIALS AND METHODS

The study includes 12 patients in chronic CHF (Table I). There were omen and 9 were men. The age ranged from 40 to 71 years. Cardiac catheterization demonstrated coronary heart disease in 7 subjects, rheumatic heart disease in four and cardiomyopathy in one subject. All patients had symptoms and signs of severe CHF (New York Heart Association class III and IV) despite conventional treatment. Mean heart size was 820 ml per m² body surface and left ventricular ejection fraction 22 %. Only 2 patients had peripheral oedemas. Mean furosemid dosage was 90 mg, and mean spironolactone dosage was 50 mg.

A Swan Ganz thermodilution catheter was after 2 hours bed rest introduced through a femoral vein to the pulmonary artery. Brachial arterial pressure was measured by sphygmomanometry. Measurements were performed in bed during 4 days. M mode echocardiograms were registered before treatment, repeated after four days and then after 6 weeks of treatment. Exercise tolerance was tested in 7 patients by bicycle ergometry before bed rest. The load was increased stepwise and total capacity expressed as joules. Five patients were unable to perform the test because of the severity of the failure.

Table I Clinical data (CHD = Coronary heart disease)

No	Age	Diagnosis	NYHA	Heart volume	Furosemide	Spironolactone
1	39	Aortic Insuff. op Mitral Insuff. op	III	1100	120 mg	75 mg
2	60	Aortic Stenosis op	III	1100	80 mg	50 mg
3	44	CHD	III	970	40 mg	75 mg
4	60	CHD	III	710	120 mg	75 mg
5	47	CHD	IV	850	120 mg	100 mg
6	49	Aortic stenosis op Mitral stenosis op	IV	670	80 mg	75 mg
7	70	CHD	III	630	160 mg	50 mg
8	57	CHD	III	690	40 mg	
9	60	Cardiomyopathy	III	1200	40 mg	
10	57	Aortic Insuff. op Mitral Stenosis op	III	720	80 mg	50 mg
11	64	CHD	IV	510	120 mg	
12	51	CHD	IV	700	80 mg	50 mg

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Echocardiographic measurements

Table II shows changes in echocardiographic measurements. After 4 days prazosin treatment the ejection fraction showed a slightly significant improvement ($p<0.05$). Cardiac index, stroke volume (SV) and V_{cf} also increased but not significantly. After 6 weeks there were no significant changes from the control recordings.

Table II Echo-cardiographic evaluation (Mean ± SEM).

	Control	4 days treatment	6 weeks treatment
EF	36±4	42±4	36±4
CI	2.9±0.3	3.3±0.5	3.1±0.6
V_{cf}	0.73±0.08	0.82±0.08	0.77±0.08

EF = Ejection Fraction in %. CI = Cardiac Index in l/min/m²
V_{cf} = Velocity of circumferential fiber shortening in circ/sec.
* $p<0.05$

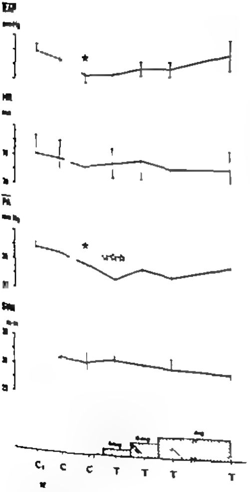

Figure 2. Hemodynamic data (II) (Mean ± SEM).
$\overline{RAP}$ = Mean right atrial pressure. HR = Heart rate
$\overline{PA}$ = Mean pulmonary arterial pressure. SWI = Stroke work index. (Other abbreviations as in Figure 1.)

The exercise test

Because 2 patients died only 5 patients performed a second bicycle exercise. All except one patient showed a small increase in working capacity; the improvement was not statistically significant (Figure 3).

Other parameters

Only one patient reported a distinct relief of symptoms. The weight increased unsignificantly from 69.9 to 71.3 kg. Electrolytes, creatinine, aldosterone and cortisol levels were unchanged.

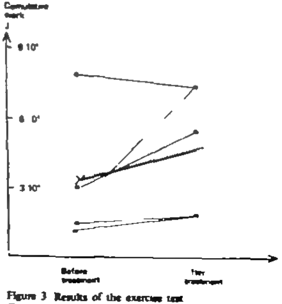

Figure 3. Results of the exercise test.
Cumulative work in joule (J) (x—x = mean)

After an observation period of 18 hours in bed prazosin was added to the conventional therapy in increasing dosage from 1 mg four times a day to 3 mg four times a day on the third day. The dosage was left unchanged until reevaluation 6 weeks later when hemodynamic measurements, echocardiography and exercise test were repeated.

RESULTS

Hemodynamic measurements

Effects of bed rest.

During 18 hours bed rest without prazosin left ventricular filling pressure (LVFP) was as shown in Figure 1 reduced from 25±3 to 19±2 mm Hg ($p<0.02$). Mean right atrial pressure $\overline{RAP}$ was as shown in Figure 2 reduced from 8±1 to 5±2 mm Hg ($p<0.05$). Mean arterial blood pressure, cardiac index, heart rate, stroke work index and systemic vascular resistance (SVR) were essentially unchanged.

Short term effects of prazosin

All values are means of several measurements during the three first days of prazosin treatment. Mean blood pressure was reduced from 88±2 to 83±2 mm Hg ($p<0.01$) without further reductions during the next two days. LVFP decreased in all patients from 19±2 to 16±2 mm Hg ($p<0.02$). However during the next two days LVFP rose despite increased dosage of prazosin. Cardiac index, heart rate and $\overline{RAP}$ were not significantly changed. SVR was reduced from 1593±154 to 1346±92 dyn sec^{-1}-cm^{-5} ($p<0.05$), without further change in the succeeding days. Stroke work index was unchanged.

Long term effects

Mean values of several measurements during the first 8 hours after catheterization procedure were compared. The group was at that time reduced to nine patients because one patient refused recatheterization and two patients were dead. Mean arterial blood pressure had increased to the level before treatment. None of the other parameters changed significantly during 6 weeks of prazosin treatment.

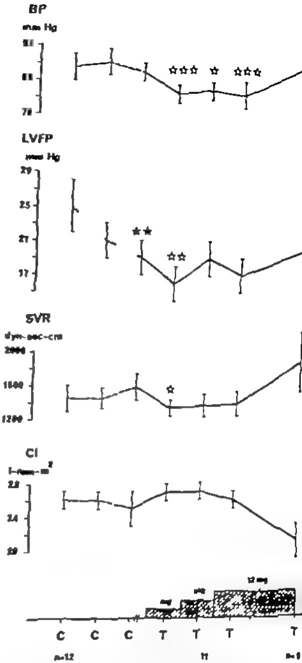

Figure 1. Hemodynamic data (I) (Mean ± SEM)
BP = Mean arterial blood pressure. LVFP = Left ventricular filling pressure.
CI = Cardiac index. SVR = Systemic vascular resistance.
C_1 = Control at start of monitoring
C_2 = Mean of control values during 8 hours
C_3 = Control after 18 hours
T_{123} = Prazosin treatment during 1st, 2nd and 3rd day
T_c = Mean of values during 8 hours after 6 weeks

★ versus C_1 $p<0.05$
★★ versus C_1 $p<0.02$
☆ versus C_3 $p<0.05$
☆☆ versus C_3 $p<0.02$
☆☆☆ versus C_3 $p<0.01$

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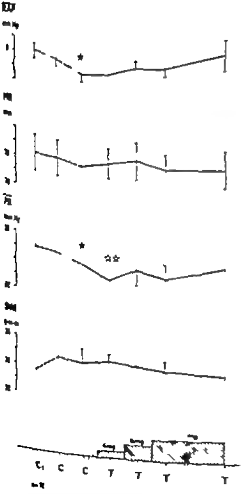

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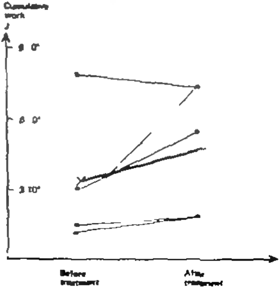

Figure 3. Results of the exercise test. Cumulative work in joule (J). (—— = mean)

SUMMING UP

The major finding of the present study was that bed rest alone causes a favourable effect on the filling pressures of the heart. The vasodilator treatment significantly reduced afterload However there was no concomitant increase of cardiac output (CO), and the effect on the left ventricle filling pressure was small and transient.

Patients with severe CHF have low myocardial compliance due to myocardial fibrosis. Therefore, the optimal sarcomer length is probably gained at a higher filling pressure than in healthy subjects After bed rest our patients probably operate on the ascending part of the Frank Starling curve explaining why prazosin reduced afterload without increasing CO In these severely ill patients the sarcomere length for optimal left ventricular function is obtained by a filling pressure which is in conflict with lung congestion.

CONCLUSIONS

1 By 18 hours bed rest preload of the left ventricle was substantially reduced

2. After the favourable effect of bed rest further reduction on resting pre and afterload with prazosin treatment was small and transient.

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DISCUSSION

Clinical efficacy of prazosin

Lessem

What happened to the patients who survived six weeks Dr Thaulow? How many of them survived one year and how many of them went back to work?

Thaulow

None of our patients went back to work. Within one year five were dead

Fischer Hansen

Did your patients improve? I am not thinking of the hemodynamics but on the patients. Did they feel better worse or unchanged?

Thaulow

Most of the patients were relieved symptomatically

Awan

The wedge pressures of about 19 and the cardiac index of about 2 9 indicates that the patients in your study were essentially very mild CHF patients Dr Thaulow why do you keep them on drug? One reason that the hemodynamics did not improve might be that the patients were too good.

Thaulow

We were wondering if vasodilator treatment had additional effects to bed rest, and in case any hemodynamic response occurred if it was beneficial to the

patients. The pressures obtained after bed rest alone was perhaps the optimal. The literature indicated beneficial effects of prazosin in increasing doses to overcome tachyphylaxia and this study was done to evaluate this phenomenon and the long term effects of the treatment.

If we are going to make further studies on vasodilators in CHF we would like to make the hemodynamic measurements during all day activity. The resting situation gives very little information about this.

Reuben

Our haemodynamic data was achieved in patients who had already been in hospital for about five days, so they did not come straight in from the out-patient clinic and had their haemodynamic study next day. The data that we are presenting is therefore, to some extent, similar to Dr Thamlow's but our patients appear to be much worse than his.

Does a low dose of prazosin prevent tachyphylaxia?

Ryden

There are fairly large differences in the amounts of prazosin given to different patients in various studies. I wonder whether large amounts of prazosin might work in another way than small amounts. Maybe the development of tachyphylaxia depend on the amount given.

Awan

It is a quite interesting question whether low or high doses of prazosin should be used. There are some data from the Peter Bent Brigham Hospital where they have looked closely at alfa$_1$ and alfa$_2$-receptors. A high dose of the agent produced increasing alfa$_2$ as well as alfa$_1$ blockade. In other words the alfa$_1$ specificity is more or less lost with increasing doses. At higher doses they think that you are getting essentially a phentolamine-like effect. If this is correct one would think that giving a lower dose would permit maintenance of the alfa$_1$ specificity and thereby perhaps retard the development of a tachyphylaxia. However in our initial studies we found no differences of importance with 1 or 2 mg. Consequently we subsequently used the higher dose. Later we became aware, as everyone else, that the acute hemodynamic responses in many cases really may not predict how the patients are going to respond long-term. At present we start with a very low dose 1 mg 3 or 4 times daily when using prazosin in clinical practise.

Reuben

We arbitrarily used 3 mg of prazosin daily. Our group of patients had a systolic arterial pressure that was not much above 100 mm Hg. We found that even with the 3 mg dose the systolic pressure was coming down to 100. I do not think the patients would have tolerated as much as 12 mg per day. In every symposium on vasodilators in CHF the haemodynamic responses in similar study protocols differ between different patients. Even though all patients have high left ventricular filling pressures and low cardiac indices, they seem to respond differently in the various studies.

Awan

I agree. The suggestion to start with a small dose and keep the patient on a small amount is maybe a very wise suggestion, particularly so if beta-stimulating drugs will be accepted in the future.

Convadson

Dr Awan, how does your last statement about the low dose of prazosin fit in with your statement from yesterday that one way to regain the effect of prazosin was to increase the dose.

Awan

The statement that I just made was based on the Harvard data. This does not necessarily represent my own opinion. Our experience has been that you can increase the dose somewhat and get a better response. In the study where we made repeated studies and maintained the patient on the same dosage one would anticipate that keeping the patient like that would not allow a spontaneous restoration of the effect if the alfa$_2$-receptor recruitment occurs. The fact that the blunting actually went away indicates to us that the lack of efficacy is a reversible, transient phenomenon. It might

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Thaulow

We were wondering if vasodilator treatment had additional effects to bed rest and in case any hemodynamic response occurred if it was beneficial to the

MANAGEMENT OF SEVERE CHRONIC CHF WITH ORAL PIRBUTEROL

Naser A. Awan, Kathleen Needham, Mark K. Evenson and Dean T. Mason*

In health and disease the performance of the heart is principally governed by the intimate integration of the four major determinants of ventricular function: heart rate, preload, ejection impedance, and myocardial contractility (Mason 1978). The singular importance of elevated left ventricular preload and raised outflow impedance has recently been recognized (1978) and several extremely beneficial afterload reducing vasodilator drugs are now available for the therapy of acute (Majid et al. 1971, Franciosa et al. 1972, Hermanovich et al. 1980) and chronic congestive heart failure (CHF) (Chatterjee et al. 1976, Awan et al. 1977, Mason et al. 1977, Awan et al. 1978). However although digitalis has been extensively used for the management of myocardial dysfunction, this agent has modest effects on cardiac pump function. Therefore, the search continues for more safe and more effective pharmacologic agents with major positive inotropic action. Accordingly we performed a series of hemodynamic and clinical investigations (Awan et al. In press, Awan et al. 1980) to evaluate the oral beta-adrenoceptor agonist drug, pirbuterol, which has combined vasodilator and inotropic (Awan et al. 1980, Mason et al. 1978, Sharma et al. 1979, Awan et al. In press) effects in patients with severe left ventricular dysfunction.

PATIENT POPULATION AND STUDY DESIGN

Nine adult patients with chronic CHF refractory despite conventional therapy with digoxin, diuretics and long acting nitrates, were included in the study population. All patients had previously documented severe three-vessel coronary disease, prior myocardial infarction with segmental ventricular dyssynergy and symptoms of CHF ranging in duration from one to six years. Symptomatically all patients were in New York Heart Association Functional Class III or early Class IV.

Initially the cardiocirculatory effects of 0.4 mg/kg of oral pirbuterol were examined by right heart catheterization and forearm plethysmography in ten patients (Awan et al. In press). Thereafter eleven patients were treated with oral pirbuterol, 0.4 mg/kg three times daily for a period of 8 weeks. Therapy with digitalis and diuretics was continued throughout the period of ambulatory evaluation of pirbuterol efficacy; the administration of nitrates was discontinued. Before and during long-term pirbuterol therapy ventricular function was assessed by nuclear scintigraphy, physical capacity by treadmill exercise testing, and symptomatic improvement was evaluated by the New York Heart Association functional classification.

ACUTE HEMODYNAMIC AND SYSTEMIC CIRCULATORY EFFECTS OF PIRBUTEROL

Cardiac Catheterization. Cardiac function was assessed by a Swan-Ganz thermodilution catheter positioned in the pulmonary artery. Thereby pulmonary artery pressures were measured directly and cardiac output (CO) was determined using iced saline solution. Systemic arterial pressures were directly recorded via a Teflon catheter introduced into the left brachial or radial artery.

Derived hemodynamic variables were calculated as follows. Stroke work index (SWI) was obtained in $g\,m/M^2$ as SI x (BP − LVFP) x 0.0136 where SI = stroke index, BP = mean systemic arterial pressure, and LVFP = left ventricular filling pressure measured either as the mean pulmonary artery wedge or pulmonary artery diastolic pressure. Total systemic vascular resistance (TSVR) was determined as 80 (BP − RA/CO), where RA = mean right atrial pressure, CO = cardiac output, and 80 converts millimeters of mer

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be possible that the alfa$_2$ recruitment is temporary but I think this is unlikely Furthermore, the blunting phenomenon that most people have observed has occurred over a period of time and not rapidly The alfa$_2$ recruitment would be anticipated to occur very rapidly in seconds as a matter of fact. I think this theory is very controversial

(p<0.001) at six hours post-PBT ingestion. Similarly the control reduced stroke volume index of 22±2.6 ml/beat/M² (Figure 2B) was raised to 29±3.2 (p<0.01) at 30 minutes and 31±3.3 (p<0.005) at 60 minutes. Thereafter the SI was 30±2.9 (p<0.001), 29±3.9 (p<0.005) and 29±4.0 ml/beat/M² (p<0.05) at two, three and four hours respectively. At five hours after oral PBT the SI was 27±3.2 (p<0.01) and remained elevated at six hours being 27±2.7 ml/beat/M² (p<0.05).

The control stroke work index of 17.8±2.7 gm m/M² (Figure 3A) was enhanced by PBT to 23.1±4.8 (p<0.01) at 30 minutes following drug ingestion. Thereafter this index of left ventricular pump function remained augmented throughout the study period being 22.0±3.6, 21.8±3.3, 22.4±4.0, 22.1±3.4, 21.3±3.4 and 20.3±3.8 at one, two, three, four, five and six hours respectively (all p<0.05). Total systemic vascular resistance was reduced by PBT (Figure 3B), the control TSVR of 2095±237 dynes sec-cm⁻⁵ falling to 1486±219 (p<0.01) at 30 minutes and decreasing further to 1274±208 (p<0.001) at one hour post PBT ingestion. This variable reached its nadir at two hours following PBT 1208±134 (p<0.001).

Thereafter TSVR gradually returned towards the control value, although substantial decline in TSVR persisted 1506±140 dynes-sec-cm⁻⁵ (p<0.001) at six hours following PBT ingestion. The index of myocardial oxygen consumption of HR SBP was unchanged by PBT (Figure 3C) throughout the six hours of measurement.

The control lowered forearm blood flow of 1.8±0.4 ml/100 g/minute was augmented by PBT to 2.4±0.5 (p<0.05) at two hours after drug ingestion (Figure 4A), while the elevated forearm vascular resistance (Figure 4B) of 52.2±6.2 mm Hg/ml/100 g/minute was decreased to 36.7±6.9 (p<0.05). Concomitantly the raised forearm venous tone of 39.9±9.1 mm Hg/ml was diminished (Figure 4C) by PBT to 17.1±5.6 (p<0.05).

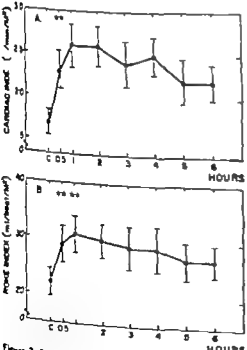

Figure 2. Sequential effects of a single dose of pirbuterol on cardiac index (Panel A) and on stroke index (Panel B) in the ten chronic CHF patients.

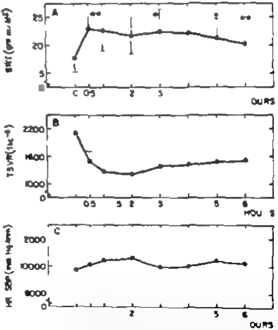

Figure 3. Sequential effects of a single dose of pirbuterol on stroke work index (SWI) (Panel A), on the total systemic vascular resistance (TSVR) (Panel B) and on the myocardial oxygen consumption index of heart rate times systolic blood pressure (HR SBP) in the ten chronic CHF patients.

cury to dynes sec-cm^5 The double product (myocardial oxygen consumption index) was obtained in mm Hg/min as SBP x HR where SBP = systolic blood pressure and HR = heart rate.

Plethysmography: Forearm plethysmography was performed by placing the mercury filled rubber strain gauge around the mid forearm as previously described (Mason & Braunwald 1962). Forearm venous occlusion was rapidly achieved by inflation of a sphygmomanometer cuff wrapped around the upper arm and attached to a container of compressed air with a special pressure gauge preset at 30 mm Hg. Forearm blood flow was calculated from the change in forearm circumference during acute venous occlusion and was expressed as milliliters per 100 gram of tissue per minute. Simultaneous intra arterial pressure was obtained from the indwelling brachial artery catheter placed in the opposite arm. Forearm vascular resistance was calculated as the ratio of BP to forearm blood flow expressed in units of mm Hg/ml/100 g/min.

Forearm venous tone was determined in all patients by the acute occlusion technic (Mason & Braunwald 1962) with an indwelling 19-gauge Teflon catheter or needle placed in a forearm vein immediately distal to the forearm strain gauge. The ratio of change in forearm venous pressure to the change in forearm volume (expressed in mm Hg/ml) that occurred during the initial 10 seconds after inflation of the upper arm venous occlusion cuff to 30 mm Hg was measured to determine the pressure volume relations of the capacitance bed.

Following the acquisition of control cardiac and peripheral circulatory hemodynamic measurements, 0.4 mg/kg of oral pirbuterol was ingested, and cardiocirculatory hemodynamic variables were repeated every 30 minutes for 6 hours in all patients.

The control heart rate of 80±4.3 beats/minute was slightly raised ($p<0.05$) by pirbuterol (PBT) to 86±3.7 beats/minute at one hour and remained mildly elevated ($p<0.05$) at this level throughout the study being 86±4.3 beats/minute at six hours following PBT ingestion. Ventricular ectopy was not induced by the agent. Mean systemic arterial blood pressure was modestly decreased by PBT (Figure 1A). Thus the control MBP of 82±5.3 mm Hg was reduced to 76±4.3 ($p<0.01$) mm Hg at 30 minutes and 73±3.2 mm Hg at one hour ($p<0.01$) remaining diminished for five hours being 73±3.2, 72±4.0, 75±4.0 and 76±4.3 mm Hg (all $p<0.05$) at two, three, four and five hours and 77±4.1 mm Hg at six hours ($p>0.05$) respectively following oral PBT ingestion.

The control elevated left ventricular filling pressure of 24±2.2 mm Hg (Figure 1B) declined to 19±2.4 mm Hg ($p<0.005$) at one hour, 20±2.8 mm Hg ($p<0.005$) at two hours, 18±2.6 ($p<0.005$) at three hours, 20±2.8 ($p<0.05$) at four hours, 20±2.6 ($p<0.005$) at five hours, and rose towards control at six hours being 22±2.3 ($p<0.05$).

The control abnormally low cardiac index of 1.7±0.16 L/min/M^2 was markedly augmented by 30 minutes after PBT ingestion to 2.3±0.23 L/min/M^2 ($p<0.01$) and rose to its peak of 2.6±0.25 ($p<0.001$) at one hour after PBT (Figure 2A). Subsequently the cardiac index remained elevated throughout the measurement period of six hours being 2.6±0.26 ($p<0.001$) at two hours, 2.4±0.27 ($p<0.005$) at three hours, 2.5±0.26 ($p<0.001$) at four hours, 2.2±0.25 ($p<0.005$) at five hours, and 2.2±0.19 L/min/M^2

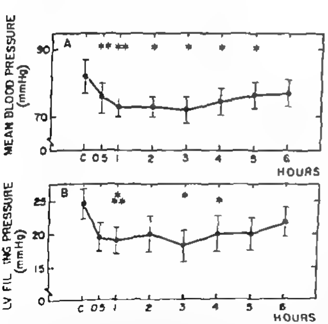

Figure 1. Sequential effects of oral pirbuterol on mean intraarterial pressure (Panel A) and on left ventricular (LV) filling pressure (Panel B) in the ten patients with chronic refractory CHF. Average values ± SEM are shown throughout the 6-hour period of evaluation following ingestion of a single dose. C = control (pre-drug). *$p<0.05$ **$p<0.01$ ***$p<0.005$ †$p<0.001$

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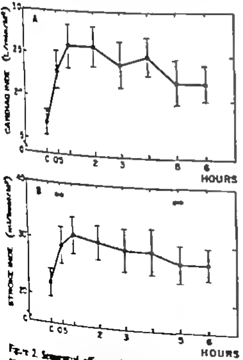

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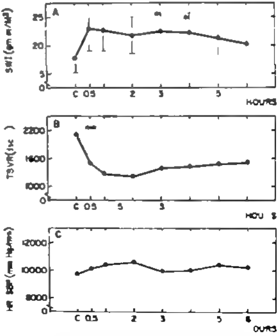

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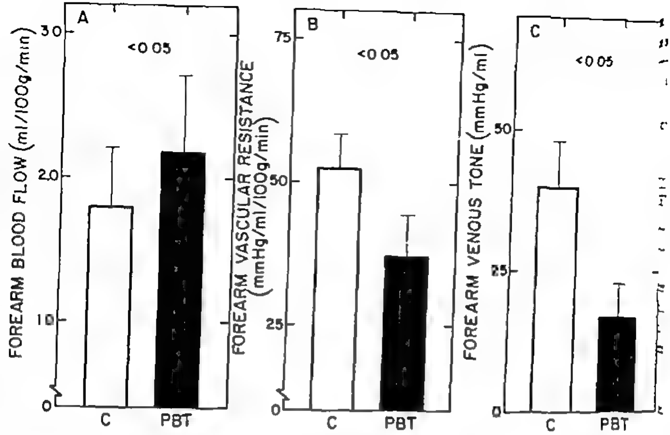


Figure 4 Effects of pirbuterol (PBT) (2 hours post-drug) on forearm blood flow (Panel A), forearm vascular resistance (Panel B) and on forearm venous tone (Panel C) in eight chronic CHF patients

LONG TERM EFFECTS OF PIRBUTEROL ON VENTRICULAR FUNCTION EVALUATED BY NUCLEAR SCINTIGRAPHY

Multigated nuclear angiography was performed in each of eleven patients using the mobile Searle low energy scintigraphic system and 37 PM tube camera with high resolution parallel hole collimator The camera was interfaced with the Medical Data Systems PAD portable computer (Medical Data Systems, Ann Arbor Michigan) to acquire the radionuclide data and display cardiac images. With the patient positioned beneath the camera, 25 mCi of technetium-99m labeled autologous red blood cells were injected intravenously After the labeled red cells reached equilibrium in the blood pool, imaging of the heart was performed Radioactive counts measured by the camera were stored in the computer by ECG gating each cardiac cycle into 14 consecutive 0.04 sec intervals. Thereby 14 frames were obtained during each cardiac cycle from end-diastole through end-systole and summed for 200 to 300 such cardiac cycles by acquiring 180,000 counts per frame. Images were collected in both the 30° right anterior oblique and left anterior oblique (LAO) projections which most clearly defined the left ventricular chamber and interventricular septum At the end of acquisition the computer was formulated to display the 14 summated frames in both views in rapid sequence to provide radionuclide cineangiography To determine ejection fraction, the left ventricle was isolated in the LAO projection and by computer technique the difference between end-diastolic counts minus end systolic counts divided by end diastolic counts was obtained.

Ventricular function was assessed by nuclear scintigraphy before and after six weeks of continuous oral pirbuterol therapy 20 mg orally three times daily Throughout this period prior therapy with maximal doses of digoxin and diuretics was kept constant while vasodilators were discontinued The control left ventricular ejection fraction was markedly depressed (Figure 5A) being 0.25±0.03 reflecting the degree of severity of the underlying myocardial dysfunction

caused by coronary disease and prior myocardial infarction in these patients. Six weeks of continuous therapy with oral pirbuterol raised the left ventricular ejection fraction to 0.29±0.04 (p<0.01). An increase in ventricular function was observed in ten of the eleven patients treated with this beta-receptor agonist agent.

LONG-TERM EFFECTS OF PIRBUTEROL ON EXERCISE TOLERANCE

Following scintigraphic estimation of ventricular function, each of the eleven patients underwent determination of maximal exercise capacity using graduated multistage treadmill exercise tests before and after six weeks of continuous oral pirbuterol therapy (20 mg orally three times daily). Although angina pectoris developed during exertion in two patients, in none of the patients was it necessary to discontinue the exercise test because of chest pain. Prior to pirbuterol therapy the average exercise capacity was 267±25 seconds (Figure 5B), all patients terminating treadmill exercise because of severe dyspnea and/or marked fatigue. After six weeks of continuous oral therapy with pirbuterol, ten of our eleven patients were able to perform exercise for a longer period, the average duration of exercise being increased by oral pirbuterol to 366±36 seconds (p<0.001).

LONG-TERM EFFECTS OF PIRBUTEROL ON SYMPTOMS

Symptomatic evaluation and physical examination of each of the eleven patients were performed before and at weekly intervals after the initiation of oral pirbuterol therapy (20 mg three times daily) for a period of six weeks. Each patient maintained a diary of symptoms, including occurrence and degree of dyspnea, fatigue, orthopnea, chest pain and related difficulties. To aid in this self-evaluation of the extent of symptoms, each patient classified dyspnea on a scale of 0 to 4 daily: 0 when none occurred, 1+ with more than ordinary activity, 2+ with ordinary physical activity, 3+ dyspnea at rest and 4+ orthopnea. In this manner dyspnea was graded along with other symptoms related to ventricular dysfunction to provide serial clinical function classification from I to IV according to the criteria of the New York Heart Association (NYHA).

The mean duration of follow-up of pirbuterol therapy was 42 days. Symptoms due to heart failure were

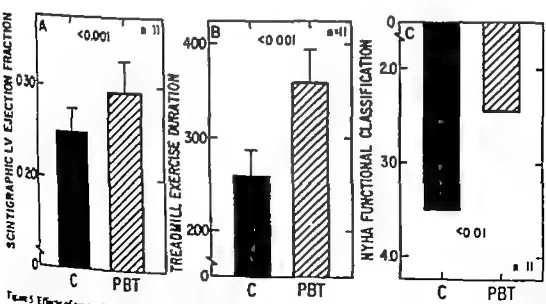
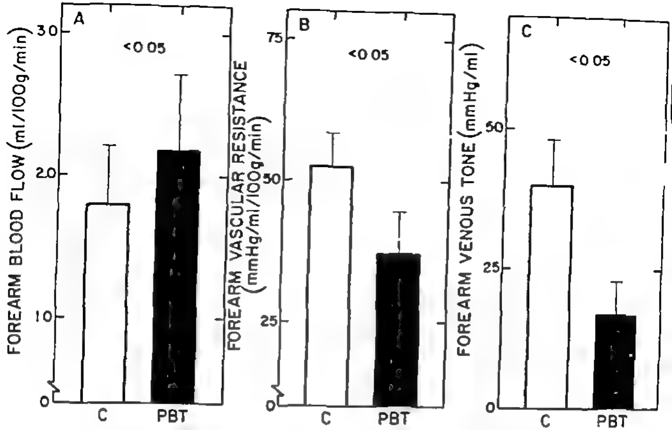


Figure 5 Effects of six week continuous oral pirbuterol (PBT) (20 mg t.i.d.) on scintigraphic ejection fraction (Panel A), treadmill exercise duration (Panel B) and New York Heart Association (NYHA) functional classification (Panel C) in eleven severe CHF patients. C = control.



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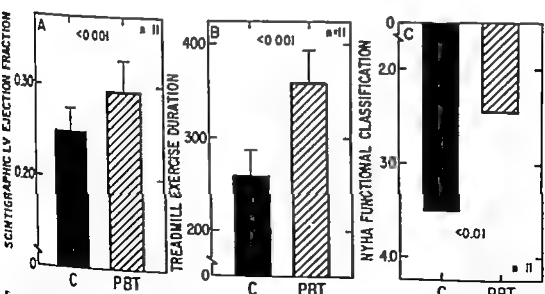

Figure 5 Effects of six-week continuous oral pirbuterol (PBT) (20 mg t.i.d.) on scintigraphic ejection fraction (Panel A), treadmill exercise duration (Panel B) and New York Heart Association (NYHA) functional classification (Panel C) in eleven severe CHF patients. C = control

greatly diminished with pirbuterol in all eleven patients (Figure 5C). Prior to initiation of pirbuterol therapy despite therapy with digoxin and diuretics, all patients had marked dyspnea and fatigue (NYHA functional class IV in five patients and class III in the remaining six patients). Figure 5C shows considerable decrease in the symptoms of CHF achieved with long term oral pirbuterol therapy in individual patients. Of the five patients in class IV prior to pirbuterol therapy the oral drug reduced CHF symptoms to class III in three and to class II in two. Similarly symptoms were diminished in the six patients from class III to class II in five and to class I in the other with pirbuterol.

CONCLUSIONS

The present study of the temporal hemodynamic effects of oral pirbuterol clearly demonstrates that this pharmacologic agent results in sustained and dramatic improvement of impaired left ventricular function in patients with chronic coronary disease. Thus, in our patients with severe CHF (mean ejection fraction of 19 %), marked augmentation of depressed pump output occurred concordantly with considerable reduction in excessive cardiac preload (Figures 1B, 2 and 3A), while mean blood pressure decreased only slightly (Figure 1A). Furthermore, since pirbuterol resulted in substantial decline in total systemic vascular resistance (Figure 3B), myocardial oxygen consumption index was unaltered (Figure 3C) despite minimal increase in heart rate.

In regard to the physiologic mechanisms of the beneficial cardiocirculatory responses to ingested pirbuterol, the principal effects appear related to the known positive inotropic action of the agent (More et al 1978) causing a remarkably enhanced CO for several hours following a single dose of this newly formulated sympathomimetic drug (Awan et al. In press, Sharma et al 1979). Further, in addition to improved cardiac contractile state, the considerable simultaneous decline in elevated left ventricular preload (Figure 1B) is partially the result of systemic venodilation (Figure 4C) produced by pirbuterol (Awan et al In press). Similarly, while the predominant means of CO augmentation is likely increased contractility effected by beta-1 agonism, the concomitant reduction in systemic vascular resistance (Figures 3B and 4B) facilitates ventricular emptying (Awan et al In press, Awan et al 1980). Although the precise magnitude of the contributions of the cardiotonic and vasorelaxant properties of pirbuterol to its resultant salutary hemodynamic actions is difficult to ascertain, it is rational that the powerful inotropic stimulation was paramount, since CO was markedly augmented while peripheral vasodilation was modest (Figures 4B and 4C).

Concerning the possible mechanisms of the reduced left ventricular preload noted in this study, a decline of end-systolic volume associated with augmented contractility and enhanced left ventricular ejection fraction is known to decrease left ventricular filling pressure (More et al 1978). Thus, the reduction in this parameter noted in some patients during dobutamine infusion (Vatner et al 1974, Beregovich et al 1975, Akhtar et al 1975, Leier et al 1977) is likely related to the aforementioned mechanism of improved ejection fraction and elevated CO. Further, oral pirbuterol causes significant decline in venous tone (Awan et al In press). Thereby reducing cardiac preload. Thus, it is probable that pirbuterol effected fall in left ventricular filling pressure is the result of augmented myocardial contractility decreasing end systolic volume combined with the beneficial venodilator actions of the drug. Nevertheless, regardless of the mechanism of this helpful decline in elevated left ventricular filling pressure, the useful preload lowering effect of pirbuterol is usually of modest magnitude. Thereby during ambulatory therapy of severe CHF our data indicate that the addition of a systemic venodilator may be necessary to optimize preload reduction in severe CHF. Further, the approach of combined therapy with vasorelaxant agents provides a potential mechanism for greater augmentation of depressed CO (Mason 1978b). That the beneficial effects of pirbuterol are additive to those of digitalis is shown in the present study by the elevation of left ventricular function caused by pirbuterol in our previously digitalized heart failure patients.

During ambulatory therapy of CHF with oral pirbuterol a marked amelioration of disabling heart failure symptomatology enabling considerable improvement in NYHA functional classification was demonstrated (Figure 5C). These subjective benefits were accompanied by objective documentation of enhancement

of cardiac function by gated blood pool radioisotope scanning (Figure 5A) and treadmill exercise performance (Figure 5B). Thus pirbuterol caused sustained augmentation of the left ventricular ejection fraction with attendant elevation of cardiac pump performance, improved functional exercise capacity, decreased fatigability and reduced dyspnea.

It is emphasized that while these salutary hemodynamic and clinical actions of oral pirbuterol are encouraging, the determination of precise therapeutic usefulness of this agent in the prolonged management of patients with severe chronic CHF must await further trials. It is noteworthy that initial experience with this agent at our institution did not demonstrate precipitation of increased ventricular ectopy or exacerbation of myocardial ischemia. The only side-effects noted were mild transient nausea and restlessness in three of the patients. Accordingly, if further controlled evaluation confirms continued efficacy and safety of this agent, the incorporation of oral pirbuterol into the pharmacological approach to the management of severe chronic CHF may provide considerable therapeutic benefit.

Acknowledgement

We acknowledge the assistance of Ms. Kathleen Hofmann

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Waagstein

There are no difficulties to show in the laboratory the pure inotropic effect of a drug and to separate that effect from a vasodilating effect. Have you any animal data on isolated muscle comparing the inotropic effects of this drug to for instance isoprenaline or noradrenaline?

Awan

The initial studies which were done with this drug in isolated muscle preparations showed a selective beta 2 stimulation. We have done haemodynamic comparisons between isoprenaline and pirbuterol. There is no question that you get a much bigger increase in CO and a much lower reduction in filling pressure but heart rate increases much more and you get much more ectopics with isoprenaline. What I am trying to say is that I think that if you give the correct dose of isoprenaline the effects will become comparable haemodynamically. Do you think a beta 1 selective agonist is preferable to a non-selective beta-agonist for treating CHF?

Waagstein

I think you partly answered this question yourself. If it is not so much a beta 1 it must be more of a beta 2 receptor stimulator. Therefore you get a lot of side-effects, for instance the tremor. I would rather have a pure beta-1 stimulator and then dilate the vessels with some different drug which does not effect the beta-2 receptors.

Reuben

We are also interested in the haemodynamic effects of oral pirbuterol in CHF and have accumulated experience in 60 patients. Once again, there was a striking difference between our experience and that of Dr Awan's. First of all we have seen no cases of tremor induced by the drug, but we have had three patients withdrawn from chronic therapy because of cramps, both in the hands and the calves. We have observed profound falls in left ventricular filling pressure amounting to 40 % as well as striking increases in CO. We are, therefore, quite enthusiastic about this drug. It gives us what we want – profound fall in filling pressure leading to less pulmonary congestion and a striking rise in CO.

Awan

All drugs have applications that can be used intelligently and carefully and usually with benefit in the majority of instances. I think pirbuterol in some patients gives a dramatic effect. In other patients you may have a remarkable increase in CO but the patient cannot handle the drug. He comes trembling back to you and the degree of tremor that sometimes occur is really dramatic.

COMPARISON OF THE VASODILATOR PRAZOSIN AND THE SELECTIVE BETA$_1$ AGONIST PRENALTEROL ON REST AND EXERCISE HAEMODYNAMICS IN CHF

Ian Hutton, Ann C Tweddel, Bruce C Bastian and R. Gordon Murray

Vasodilator therapy has been demonstrated to improve ventricular performance in patients with congestive heart failure (CHF) (Chatterjee & Parmley 1977 Miller *et al* 1977) Oral prazosin has been shown to exert dilating effects on both capacitance and resistance vessels and has been demonstrated by Awan *et al* 1978, Miller *et al* 1977 and Mehta *et al* 1978 to be effective in increasing cardiac output (CO) and reducing left ventricular filling pressure in patients with acute and chronic CHF

Inotropic agents can also be of value in improving cardiac performance but side-effects can be troublesome. Isoprenaline is a potent beta-adrenoreceptor agonist but provokes tachycardia and can precipitate arrhythmias (Loeb *et al* 1973) The deleterious side-effects of the sympathomimetic amines have stimulated research into newer pharmacological compounds which have inotropic effects but little or no chronotropic action. Dobutamine has been shown to have significant inotropic properties (Gillespie *et al* 1977) and in patients after open heart surgery a chronotropic action similar to isoprenaline was found in addition to the inotropic effect

The endogenous catecholamine dopamine has been shown to be a useful inotropic agent and in addition dilates renal cortical and splanchnic vessels (Goldberg *et al* 1977) However like isoprenaline, it may produce tachycardia and ventricular arrhythmias All of these compounds have to be given parenterally and a compound which can be given orally would clearly be of advantage to patients with chronic CHF

Prenalterol (S-(-)-1-(4-hydroxyphenoxy)-3 isopropylamino propanol-2 hydrochloride is a new selective β_1 adrenoreceptor agonist which has been described as having potent inotropic effects with little chronotropic action (Carlsson *et al* 1977) Johnsson *et al* 1978 have reported in human volunteers that prenalterol when administered either orally or intravenously produced an increase in myocardial contractility with little or no increase in heart rate. Arinsego *et al* 1979 have confirmed these findings in patients with acute myocardial infarction and in addition suggested that prenalterol was a useful antidote to the unwanted cardiac effects of beta-adrenoreceptor blocking drugs Hutton *et al* 1980 studied the haemodynamic effects in patients with coronary heart disease using both invasive and non-invasive methods and concluded that prenalterol enhanced the contractile state of the myocardium without altering heart rate. Reiz & Friedman 1980 have reported that prenalterol is of value in improving the haemodynamic status of hypotensive patients with gram negative septic shock.

The object of this study was to compare the effects of prazosin and prenalterol on rest and exercise haemodynamics in two groups of patients with chronic CHF

PATIENTS AND METHODS

Eighteen patients with chronic CHF despite treatment with digitalis and diuretics, were studied. Five patients had primary myocardial disease with congestive cardiomyopathy and the remainder had coronary heart disease. The diagnosis in all patients was established by left ventriculography and coronary angiography Nine of the patients with coronary heart disease had had coronary bypass surgery with either left ventricular remodelling or resection of scar tissue Symptomatically all of the patients in the prazosin group were Class III or IV of the New York Heart Classification. The patients in the prenalterol group were in Class III.

A thermodilution catheter was inserted into the Right subclavian vein percutaneously and advanced into the right main pulmonary artery Pressures were

*From the University Department of Medical Cardiology Royal Infirmary Glasgow, Scotland

Waagstein

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Prazosin in a dosage of 4 mg was then infused over a 30 minute period and haemodynamic measurements and angiography were repeated. Statistical analysis used was the Students' paired t-test, a P value of <0.05 being regarded as significant.

RESULTS

Patient group

The detailed haemodynamic results are shown in Table I and are illustrated in Figure 1.

Heart rate was 100±4 beats/min initially and was little changed by prazosin 102±5 beats/min. Systemic blood pressure fell but not significantly – systolic blood pressure being 112±12 and 96±4 mm Hg and diastolic B.P. being 66±12 and 54±16 mm Hg. There were however significant increases in cardiac index and stroke volume index from 1.6±0.1 to 2.1±0.2 L/min/m² ($p<0.02$) and from 17.2±2 to 20.4±3 ml/beat/m² ($p<0.02$). There was an associated reduction in left ventricular filling pressure from 26±4 to 18±3 mm Hg ($p<0.05$). Aortic impedance would appear to be reduced by prazosin as the systemic vascular resistance fell by 20 % ($p<0.01$). Four patients were

Table I. Haemodynamic effects of prazosin.

	Control	Maximum response
Heart rate (beats/min)	104±4	102±5
Systolic blood pressure (mm Hg)	112±12	96±4
Diastolic blood pressure (mm Hg)	66±12	54±16
Cardiac index (L/min/m²)	1.6±0.1	2.1±0.2 ($p<0.02$)
Stroke index (ml/m²)	17±2	20±3 ($p<0.02$)
Pulmonary capillary wedge (mm Hg)	26±4	18±3 ($p<0.05$)
Systemic vascular resistance (units)	25±3	18±3 ($p<0.02$)

Results are mean ± SEM in 10 patients

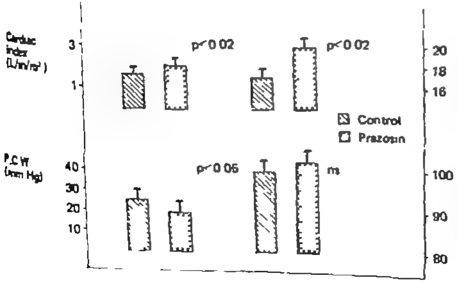

Figure 1. The haemodynamic effects of oral prazosin on cardiac index, stroke volume index, heart rate and left ventricular filling pressure as measured by the pulmonary capillary wedge pressure (P.C.W.).

recorded using electronic transducers with the zero set at mid-chest and recorded on a Mingograf 82 recorder. Cardiac output was measured in triplicate by the thermodilution technique using an Instrumentation Laboratories cardiac output computer (Ganz & Swan 1972). Blood pressure was measured using a sphygmomanometer and the heart rate was obtained from a continuous recording of the electrocardiogram. Functional exercise capacity was determined using a bicycle ergometer in four of the prazosin patients and in all eight of the prenalterol patients.

RADIONUCLIDE VENTRICULOGRAPHY – DATA ACQUISITION AND ANALYSIS

Radionuclide ventriculography was performed following red cell labelling with 20 mCi Tc^{99m} Pyrolite. Imaging was performed using an IGE Maxi-Camera II with a high sensitivity converging collimator interfaced to a Varian 620L computer. The camera was placed over the praecordium in the LAO projection which provided optimal septal separation of right and left ventricular activity and with 6° caudal tilt to exclude left atrial activity. Image data were acquired in list mode with simultaneous ECG signal recording. Sixteen images per cardiac cycle were reconstructed on a 32x32 matrix with approximately 200 000 counts per image. The local R R interval average was used to exclude premature beats.

The end-diastolic frame was displayed and a region drawn to exclude right ventricular activity and include left ventricular and adjacent activity. The pixel with maximum counts within this region was identified and accepted as the left ventricular (L.V.) maximum. An area for background correction was defined as the region formed by those pixels where count densities lay between 50 % and 55 % L.V. maximum. This area inscribed an arc in close proximity to the L.V. free wall. Left ventricular ejection fractions were calculated for a series of L.V. margins ranging from 60 % to 100 % of L.V. maximum at 2 % increments using the equation.

$$EF = \frac{(EDC - BG_D) - (ESC - BG_S)}{(EDC - BG_D)}$$

where EF = Total left ventricular ejection fraction
EDC = End diastolic counts
ESC = End systolic counts.
BG_D = End-diastolic background activity
BG_S = End systolic background activity

Each ejection fraction was plotted against the corresponding percentage value used to identify the left ventricular margin producing a characteristic curve with abrupt change in ejection fraction as the left ventricular cavity was entered. The value just prior to the inflection of the curve was taken as left ventricular ejection fraction. Calculated variables were:

Systemic vascular resistance =
(SVR) units

$$\frac{M.A.P. - R.A.P. \text{ (mm Hg)} \times 80 \text{ dyne.sec. cm}^{-5}}{C.O. \text{ } (L/min)}$$

M.A.P. = Mean arterial pressure (mm Hg)
R.A.P. = Right atrial pressure (mm Hg)
C.O. = Cardiac output (L/min).

Left ventricular stroke work index =
(L.V.S.W.I.) G–M/m²
= (M.A.P.–L.V.E.D.P.) x S.I. x 0.0136

L.V.E.D.P. = Left ventricular end diastolic pressure (mm Hg).
S.I. = Stroke index (ml/beat/m²)
C.I. = Cardiac index (L/min/m²).

PROTOCOL

Cardiac glycosides were discontinued for one week and diuretic therapy for a 24-hour period prior to the commencement of the study. In the *Prazosin* group control haemodynamic measurements were made at rest and exercise where possible and prazosin was administered orally in a dosage of 0.5 mg b.d. and thereafter titrated against the haemodynamic response to a maximum of 8 mg daily. Haemodynamic measurements were repeated over a 72 hour period.

In the *Prenalterol*-group control haemodynamic measurements were made at rest and during exercise. In addition radionuclide angiography was carried out

Prazosin in a dosage of 4 mg was then infused over a 30 minute period and haemodynamic measurements and angiography were repeated. Statistical analysis used was the Students' paired t-test, a P value of <0.05 being regarded as significant.

RESULTS

Prazosin group

The detailed haemodynamic results are shown in Table I and are illustrated in Figure 1.

Heart rate was 100±4 beats/min initially and was little changed by prazosin 102±5 beats/min. Systemic blood pressure fell but not significantly – systolic blood pressure being 112±12 and 96±4 mm Hg and diastolic B.P. being 66±12 and 54±16 mm Hg. There were however significant increases in cardiac index and stroke volume index from 1.6±0.1 to 2.1±0.2 L/min/m² (p<0.02) and from 17.2±2 to 20.4±3 ml/beat/m² (p<0.02). There was an associated reduction in left ventricular filling pressure from 26±4 to 18±3 mm Hg (p<0.05). Aortic impedance would appear to be reduced by prazosin as the systemic vascular resistance fell by 20 % (p<0.01). Four patients were

Table I Haemodynamic effects of prazosin

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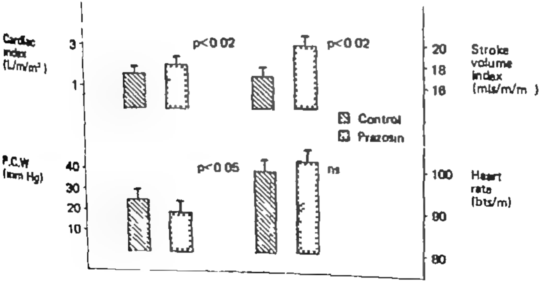

Figure 1 The haemodynamic effects of oral prazosin on cardiac index, stroke volume index, heart rate and left ventricular filling pressure as measured by the pulmonary capillary wedge pressure (P.C.W.).

able to exercise (*Figure 2*) It can be seen that after prazosin cardiac index increased from 2.1±0 2 to 3.6±0.3 L/m/m² compared with 1.5±0 1 and 2.6±0.2 L/m/m² before prazosin This increase in CO was achieved by a modest increase in L.V filling pressure compared with control measurements

Prenalterol group

The detailed haemodynamic measurements are found in Table II and Figures 3-5 (next page)

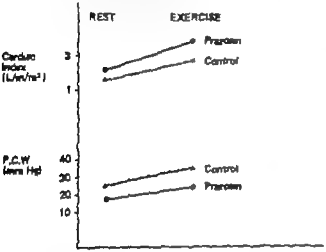

Figure 2 The haemodynamic effects of oral prazosin on cardiac index and pulmonary capillary wedge pressure P C.W during exercise on a bicycle ergometer It can be seen that there is a reduction in P C W during exercise with a greater increase in cardiac index

At rest prenalterol increased cardiac index from 1 7±0 1 to 2.0±0 1 L/m/m² ($p<0.025$). This was largely a heart rate response and stroke index was little changed 23±2 and 24±2 ml/m² Heart rate increased modestly but significantly from 75±6 to 87±5 beats/min ($p<0\,01$). There was a significant increase in systolic blood pressure from 121±7 to 132±5 mm Hg ($p<0\,01$) but diastolic pressure was unchanged 74±5 and 73±4 mm Hg. Left ventricular filling pressure fell slightly from 19±2 to 17±2 mm Hg. Left ventricular ejection fraction increased from 24±4 to 28±4 %

On exercise prenalterol increased cardiac index from 2.7±0 2 to 3 4±0.3 L/min/m² ($p<0\,05$) and stroke index from 25±3 to 31±3 ml/beat/m² ($p<0\,05$) There was no change in heart rate 111±8 and 112±5 beats/min There was slight changes in blood pressure – systolic B P being 156±15 and 166±17 mm Hg and diastolic B P being 82±8 and 76±11 mm Hg There was a significant reduction in L.V filling pressure from 33±6 to 26±3 mm Hg ($p<0\,05$).

CONCLUDING REMARKS

This study has demonstrated that prazosin and prenalterol enhance the cardiac performance of patients with CHF Prazosin would appear to reduce both impedance and left ventricular filling pressure resulting

Table II Haemodynamic effects of prenalterol

	Rest		Exercise	
	Control	Prenalterol	Control	Prenalterol
Heart rate (beats/min)	75±6	87±5 (p<0 01)	111±8	112±5
Systolic blood pressure (mm Hg)	121±7	132±5 (p<0 01)	156±15	166±17
Diastolic blood pressure (mm Hg)	74±5	73±4	82±8	76±11
Cardiac index (L/mm/m²)	1 7±0 1	2.0±0 1 (p<0 025)	2 7±0 2	3 4±0 3 (p<0 05)
Stroke index (ml/m²)	23±2	24±2	25±3	31±3 (p<0 05)
Pulmonary capillary wedge (mm Hg)	19±2	17±2	33±6	26±3 (p<0 05)
Stroke work index (G–m/m²)	22 7±4	24 7±3	26±4	33±5
Ejection fraction (%)	24±4	28±4		

Results are mean ± SEM of 8 patients

as an increased CO and SV. Prenalterol's action is largely inotropic with some chronotropic effect at rest but on exercise there was no alteration in heart rate and there were significant increases in CO and SV. Neither of the compounds were found to be arrhythmogenic in this small group of patients since no arrhythmias were detected despite continuous electrocardiographic monitoring.

Inotropic agents have been used in conjunction with vasodilators to improve cardiac performance and the combination of dopamine and nitroprusside has been shown to be better than nitroprusside alone (Stemple et al 1978, Miller et al. 1977). Prenalterol is now available in an oral preparation and the combination of these two oral compounds should be of value in the management of patients with CHF.

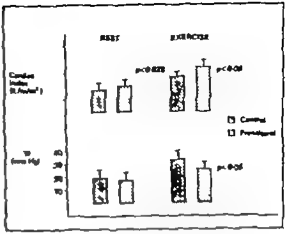

Figure 3. The haemodynamic effects of i.v. prenalterol on cardiac index and pulmonary capillary wedge pressure, P.C.W. at rest and during exercise

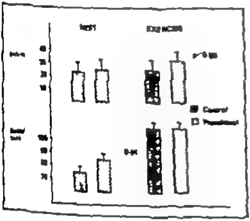

Figure 4. The haemodynamic effects of prenalterol on stroke volume index and heart rate at rest and during exercise

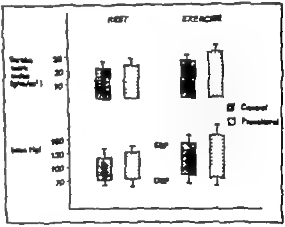

Figure 5. The haemodynamic effects of prenalterol on stroke volume index and blood pressure, both systolic (SBP) and diastolic (DBP) at rest and during exercise

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DISCUSSION

Waagstein

Was the exercise on prenalterol performed in the supine or in the sitting position?

Hutton

The patients exercised sitting upright on a bicycle ergometer These patients are incapable of doing much exercise and we were interested in the haemodynamic response to an individualised constant workload which was the same at each occasion.

Waagstein

When we made a similar study with the patient in the supine position with a workload of 50 % of their maximum capacity we did not find any increase in CO after prenalterol Otherwise our results are completely similar to yours. In fact we did not see any change in heart rate at the second exercise. In our study we used a higher dose of prenalterol, about 8 mg

Swedberg

It was said by Andersson (page 69) and also by others that prenalterol did not have chronotropic effect and I must clarify that point Prenalterol certainly has a *marked chronotropic* effect but that effect is compensated for by the baroreceptor reflex mechanism which have a vagal influence on the heart That can be illustrated by your findings where an increase in the pulse amplitude was found If you give atropine to these patients they certainly will have a very marked increase in heart rate

BENEFICIAL EFFECTS OF PROSTAGLANDIN E_1 ON MYOCARDIAL ENERGETICS AND PUMP PERFORMANCE IN SEVERE CHF

Yaron A. Awan, Kathleen E. Needham, Mark K. Evenson, John Hermanovich, Marc Gradman and Dean T. Mason

Although sodium nitroprusside is regarded as the standard intravenous vasodilator for the vasodilator therapy of acute and chronic congestive heart failure (CHF) (Majid et al. 1971, Franciosa et al. 1972, Chatterjee et al. 1973a, b, Miller et al. 1975, Miller et al. 1976), the usefulness of this drug during active myocardial ischemia following acute myocardial infarction (AMI) remains controversial (DaLuz et al. 1975, Awan et al. 1976, Chiariello et al. 1976). Furthermore increasing thiocyanate levels represent a persistent concern limiting the use of prolonged nitroprusside infusions (Lopez et al. 1979). Therefore, we evaluated cardiocirculatory actions of the vasodilator and platelet disaggregatory agent (Gorman 1978, Needleman & Kaley 1978), prostaglandin E_1, by cardiac catheterization and forearm plethysmography in patients with extensive coronary artery disease and severe CHF.

METHODS

A. Study group.

The study group comprised twelve patients, ten males and two females, with a mean age of 58.6 years. The etiology of severe chronic CHF (mean left ventricular ejection fraction 0.23) was previously demonstrated coronary artery disease with remote myocardial infarction (> 3 months) documented clinically, electrocardiographically and angiographically. Patients with significant valvular heart disease were excluded from the study. All patients were taking maximum doses of digoxin and diuretics. Each patient received the usual dose of diuretics on the evening prior to the investigation and regular dose of digoxin on the morning of the evaluation.

B. Cardiac catheterization and plethysmography.

All twelve patients underwent right heart catheterization with placement of the balloon-tipped thermodilution Swan-Ganz catheter in the pulmonary artery for assessment of cardiac performance. Forearm plethysmography was performed in seven of these patients, using a mercury filled rubber strain gauge placed around the mid-forearm as previously described (Miller et al. 1976, Mason & Braunwald 1962).

C. Prostaglandin E_1 infusion.

After control hemodynamics and cardiac output (CO) were recorded and control forearm plethysmography was performed, prostaglandin E_1 (PGE_1) was gradually infused through a peripheral vein, starting at the low dose of 0.01 μg/kg and slowly titrating the dose upwards in increments of 0.005/μg/kg under constant hemodynamic and electrocardiographic monitoring. Upward titration of PGE_1 was terminated and constant infusion rate was maintained when optimum hemodynamics (> 20 % increase in CO and/or > 20 % decrease in LVFP) were obtained. Following 15 minutes of this constant optimum dose PGE_1 infusion (mean dose 0.06 μg/kg) hemodynamics and CO were again recorded and forearm plethysmography was repeated.

RESULTS

The control heart rate of 69±2 bpm was unchanged by PGE_1 being 71±1 bpm ($p > 0.05$) during infusion of this drug.

Mean systemic blood pressure was modestly reduced by PGE_1. The average MBP declined from the control of 85±6 mm Hg to 76±5 mm Hg ($p < 0.025$). A mild decline in this variable was noted in the majority of our CHF-patients. Additionally the LV filling pressure of 19±3 mm Hg was reduced by PGE_1 to 15±2 mm Hg ($p < 0.01$). This moderate reduction in LVFP was noted in seven of our nine patients.

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*From the Departments of Medicine and Physiology, University of California, California, U.S.A.

The control cardiac index of 1 9±0.2 l/min/m² was augmented by PGE_1 to 2.5±0.2 (p <0 005). A marked increase in CI was seen in the *majority of our patients*, the average percent increase being 37 % Similarly the stroke volume index of 28±2.4 ml/beat/m² was elevated by PGE_1 to 35±2.9 (p<0 01) Substantial increase in this index was also observed in most of the patients studied

PGE_1 raised the stroke work index from 26±4.3 to 30±4 4 gm.m m² (p<0 02) *while total systemic* vascular resistance declined from 1862±192 to *1282±100 dynes-sec-cm⁻⁵ (p<0 02) The indirect* index of myocardial oxygen consumption, HR SBP product was reduced by PGE_1 from 9492±666 to 8278±493 mm Hg/min (p<0 02) while the effective endocardial perfusion pressure (diastolic BP LVFP) an index of myocardial perfusion, remained unchanged (control 47±5 PGE_1 44±5 mm Hg, p>0 05). Thus, improvement in myocardial oxygenation likely occurred with PGE_1 infusion.

Forearm blood flow (FBF) was raised by PGE_1 *from* 2.5±0 5 to 3 4±0 5 ml/100 gm/min (p<0 05) and forearm vascular resistance was reduced by PGE_1 from 36 1±5.3 to 23 7±3 7 mm Hg/ml/100 gm/min (p<0 02) but forearm venous tone remained unchanged (control 18 8±2.9 PGE_1 20 1±3 1 mm Hg/ml p>0 05).

DISCUSSION

The results of this investigation of the hemodynamic actions of prostaglandin E_1 clearly demonstrated that this agent markedly augments cardiac performance in patients with severe chronic CHF Moreover this enhancement in cardiac performance was accomplished with improved myocardial oxygenation since the double product diminished while myocardial perfusion was maintained Additionally PGE_1 raised myocardial pump efficiency as increased ventricular work was performed with less oxygen requirement. Further this impressive modulation of cardiac function coincided with simultaneous concordant beneficial modification of peripheral circulatory function of reduced vascular resistance and enhanced peripheral blood flow

The mechanism of these highly advantageous improvements in cardiac function probably relates to the vascular relaxing actions of prostaglandin E_1 on the arteriolar resistance bed (Gorman 1978). Thereby decrease in left ventricular output impedance facilitates cardiac emptying, augmenting the ejection fraction and raising the CO Further enhancement in cardiac contractility while possible (Solotkoff *et al* 1979), likely represents a less important mechanism for the marked augmentation of ventricular pump performance observed in our patients with severe CHF Importantly our observation of no significant relaxing *effects of prostaglandin* E_1 *on the systemic capacitance* bed is consistent with the moderate decrease in ventricular preload observed in this study *Indeed, it is* likely that the modest decline in left ventricular filling pressure noted in our patients during PGE_1 infusion reflects an indirect effect of the enhanced left ventricular ejection fraction. Additionally *relief of myo*cardial ischemia in our coronary heart failure patients may have improved ventricular compliance contributing to the observed fall in the elevated left ventricular filling pressure. Further prostaglandin E_1 may have *caused marked venodilation in certain peripheral vas*cular beds thereby lowering the abnormally elevated ventricular preload in our severe heart failure patients

Thus the careful use of modest doses of prostaglandin E_1 i patients with marked left ventricular dysfunction caused by severe coronary heart disease may produce a marked augmentation of cardiac performance. Thus our results indicate that prostaglandin E_1 may be beneficial for the therapy of acute and chronic severe CHF

SUMMARY

To provide more effective vasodilator agents for the therapy of severe left ventricular (LV) failure the cardiocirculatory actions of prostaglandin E_1 (PGE_1) were evaluated in nine coronary patients. PGE_1 infusion modestly decreased mean systemic blood pressure (85 to 76 mm Hg, p<0 025) and LV filling pressure (19 to 15 mm Hg p<0.01) while heart rate was unchanged (p>0 05). Simultaneously *PGE₁* augmented cardiac index from 1 9 to 2 5 l/min/m² (p<0 005), raised stroke index from 28 to 35 ml/beat m² (p<0 01) and increased stroke work index from 26 to 30 g–m/m² (p <0 02) Additionally total systemic vascular resistance decreased from 1862 to 1282 dynes sec-cm⁻⁵ (p<0 02) and double product of heart rate and systolic

blood pressure diminished from 94±2 to 82±8 mm Hg ($p<0.02$) while the effective endocardial perfusion pressure was maintained ($p>0.05$). Concomitantly forearm vascular resistance fell, forearm blood flow was raised, and forearm venous tone remained unchanged.

Thus, our results demonstrate that PGE_1 is a potent arteriolar vasodilator with markedly beneficial effects on myocardial energetics and on cardiac function in patients with severe ischemic congestive cardiac failure.

Acknowledgement
We acknowledge the assistance of Ms. Raya Drahun and Ms. Kathleen Hofman.

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DISCUSSION

Sandberg:
One advantage with prostaglandine E 1 could be the effect on the platelets. I wonder if you measured any degradation products from the platelets.

Awan:
I quite agree with you that platelet deaggregation is probably a very important part of the response to prostaglandine E 1 but this was a very preliminary study

The control cardiac index of 1.9 ± 0.2 l/min/m^2 was augmented by PGE_1 to 2.5 ± 0.2 ($p < 0.005$). A marked increase in CI was seen in the majority of our patients the average percent increase being 37 %. Similarly the stroke volume index of 28 ± 2.4 ml/beat/m^2 was elevated by PGE_1 to 35 ± 2.9 ($p < 0.01$). Substantial increase in this index was also observed in most of the patients studied.

PGE_1 raised the stroke work index from 26 ± 4.3 to 30 ± 4.4 gm m m^2 ($p < 0.02$) while total systemic vascular resistance declined from 1862 ± 192 to 1282 ± 100 dynes-sec-cm^{-5} ($p < 0.02$). The indirect index of myocardial oxygen consumption HR SBP product was reduced by PGE_1 from 9492 ± 666 to 8278 ± 493 mm Hg/min ($p < 0.02$), while the effective endocardial perfusion pressure (diastolic BP LVFP) an index of myocardial perfusion remained unchanged (control 47 ± 5 PGE_1 44 ± 5 mm Hg $p > 0.05$). Thus, improvement in myocardial oxygenation likely occurred with PGE_1 infusion.

Forearm blood flow (FBF) was raised by PGE_1 from 2.5 ± 0.5 to 3.4 ± 0.5 ml/100 gm/min ($p < 0.05$) and forearm vascular resistance was reduced by PGE_1 from 36.1 ± 5.3 to 23.7 ± 3.7 mm Hg/ml/100 gm/min ($p < 0.02$) but forearm venous tone remained unchanged (control 18.8 ± 2.9 PGE_1 20.1 ± 3.1 mm Hg/ml $p > 0.05$).

DISCUSSION

The results of this investigation of the hemodynamic actions of prostaglandin E_1 clearly demonstrated that this agent markedly augments cardiac performance in patients with severe chronic CHF. Moreover this enhancement in cardiac performance was accomplished with improved myocardial oxygenation since the double product diminished while myocardial perfusion was maintained. Additionally PGE_1 raised myocardial pump efficiency as increased ventricular work was performed with less oxygen requirement. Further this impressive modulation of cardiac function coincided with simultaneous concordant beneficial modification of peripheral circulatory function of reduced vascular resistance and enhanced peripheral blood flow.

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Thus the careful use of modest doses of prostaglandin E_1 in patients with marked left ventricular dysfunction caused by severe coronary heart disease may produce a marked augmentation of cardiac performance. Thus, our results indicate that prostaglandin E_1 may be beneficial for the therapy of acute and chronic severe CHF.

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Thor Björn Conradson and Lars Rydén

Hydralazine, like many other vasodilating agents, have been shown to improve various hemodynamic parameters in patients with chronic congestive heart failure (CHF) (Chatterjee *et al.* 1976, Fitchett *et al.* 1979). Most studies only report on the acute hemodynamic effects and there is considerably less information available about the long-term efficacy. It is of course important to document a sustained response since continuous administration of a drug without the intended circulatory effect would add nothing but a possible degree of side-effects. The present study was designed to evaluate the hemodynamic effects at rest of oral hydralazine used in the treatment of CHF acutely as well as after long-term therapy.

MATERIAL AND METHODS

Twelve patients, eleven males and one female, with CHF were investigated. All were optimally treated with digitalis and diuretics when studied. Their age ranged from 52 to 69 years and the duration of CHF from 1 to 5 years. The etiology of CHF was ischemic heart disease in five, rheumatic heart disease in two, non-rheumatic mitral regurgitation in two, alcohol cardiomyopathy in one, primary congestive cardiomyopathy in one and arterial hypertension in one patient. At the time of the investigation four patients were in NYHA class II, seven in class III and one in class IV.

A thermodilution catheter was percutaneously inserted into the pulmonary artery via a brachial vein. With this catheter cardiac output (CO), right atrial (RA) and pulmonary artery (PA) pressures were measured. Brachial artery (BA) pressure was measured by means of the standard cuff method. Systemic vascular resistance (SVR) was calculated as $\overline{BA}$ $\overline{RA}$/CO and expressed in arbitrary units. Cardiac index (CI) was calculated as CO/m^2 BSA.

With the catheter in place and after a resting period of 30 minutes a single dose of oral hydralazine was given – 50 mg to seven patients and 75 mg to five patients. The hemodynamic response was followed during five hours with the first measurement performed just prior to hydralazine intake.

All patients were investigated in the sitting position in a comfortable chair. The study was started in the morning with the patient in a postabsorptive, non-sedated state. Concomitant medication was given according to the schedule of the individual patient. A light meal without coffee or tea was served following three hours after hydralazine intake. Following the first invasive study the patients left hospital on hydralazine 150–225 mg/day on a t.i.d. basis, added to their conventional therapy. Four to five months later they were readmitted to the ward and a second invasive study was performed according to the same protocol. During the period between study one and two they were regularly seen in the out-patient clinic.

Statistical analysis was performed using the paired Student's t-test model. A p-value of less than 0.05 was accepted as statistical significance.

RESULTS

First invasive study

Hydralazine caused an increase in CI of about 40 % compared to the control value. This increase was mainly due to an improved stroke volume (+30 %). There was, however, a definite rise in heart rate, too (+20 %). Since BA-pressure did not change, SVR decreased significantly (–29 %).

Follow-up

During the follow-up period three patients died, two from sudden death and one in progressive CHF. One patient experienced an increase in dyspnea and gained

*From the Department of Medicine, Central Hospital, Skövde, Sweden.

in which we were looking at haemodynamics. As you know measuring platelet degradation is not easy There is a very large error in estimations and therefore we did not really want to get into that in this study

Holmgren
What is the half time for the duration of effect when you stop the infusion?

Awan
I cannot give you an exact figure but in terms of haemodynamic response it takes about five minutes for the response to completely disappear

Rydén.
Do you think that this type of drug is something which might give us improved therapeutic possibilities in the future?

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I think that the drug because of the platelet deaggregation aspects may be very useful in patients with acute myocardial infarction.

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Hydralazine is a rather pure arteriolar vasodilator and as such an afterload reducing agent (Åblad 1963). The positive effects obtained in treatment of CHF has been shown in acute studies by different investigators (Chatterjee *et al.* 1976, Franciosa *et al.* 1977). Recently Chatterjee *et al.* (1980) *could also report of sustained* beneficial hemodynamic effects of hydralazine in eleven patients with CHF treated for over 8 months. These investigators found an increase in CI acutely and chronically of 56 % and 65 % respectively compared to 40 % in our own study. This difference is probably dose-dependent. Thus we used 150–225 mg/day compared to 200–400 mg/day in the study of Chatterjee and co-workers.

Heart rate usually increases in patients with CHF probably as a *compensatory mechanism. Administration* of an arterial vasodilator ordinarily is expected to result in a baroceptor reflex tachycardia. To some extent this also happened in our first study where heart rate increased about 20 % (Figure 4). However when the patients *were reinvestigated heart rate was* from the beginning *lower than in the first study and* the increase following hydralazine was less pronounced (Figure 4). The reason for this favourable response following chronic treatment is unknown but one might hypothesize that an improved circulation results in decrease in the compensatory increased sympathetic *drive*.

Administration of a vasodilator is also expected to give rise to a blood pressure fall. Patients in CHF however usually do not show this response (Chatterjee *et al.* 1976). This was also found in our study where no fall in blood pressure occurred, neither acutely nor *following chronic treatment* (Figure 5). This finding together with the increase in CI at both occasions following hydralazine means that SVR, as expected, fell. Furthermore, the finding of a higher CI 12–14 hours after hydralazine in the second study indicates a *sustained afterload reduction and it might even* be possible to administer hydralazine twice daily in patients in CHF.

CONCLUSION

In conclusion, hydralazine administered to patients in chronic CHF produces positive hemodynamic effects acutely which seem to be sustained when the drug is used *as maintenance therapy. It needs to be stressed that our findings are related to resting* hemodynamics and actually our patients did not improve symptomatically according to the NYHA-classification. Therefore, there is a need for repeated invasive investigations not only at rest but, perhaps more important, also during physical exercise.

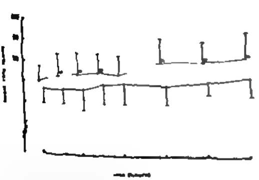

Figure 4. Heart rate (HR) before (C) and following oral hydralazine (*p<0.05)

first invasive study
second invasive study

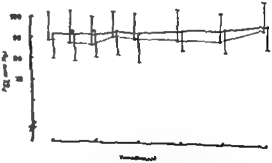

Figure 5. Mean brachial artery pressure ($\overline{BA}$) before (C) *and following oral hydralazine* (*p<0.05)

first invasive study
second invasive study

weight i.e. symptoms probably related to fluid retention. This patient stopped treatment with hydralazine by himself. Another patient refused reinvestigation why altogether seven patients were eligible for re-catheterization. In two of these seven patients a dose reduction was necessary because of drug related side-effects. During the follow up period these seven patients were stable within their NYHA-class and did not experience any significant symptomatic improvement.

Second invasive study

Prior to the morning dose of hydralazine, i.e. 12–14 hours after intake of the previous dose, CI was significantly higher (Figure 1) and SVR significantly lower (Figure 2) than the corresponding values in the first study. Following hydralazine the hemodynamic response was very similar to that of the first study with respect to CI (Figure 1) this time however more caused by an increase in stroke volume (SV) (Figure 3) than in heart rate (Figure 4). This favourable hemodynamic response remained throughout the 5-hour period.

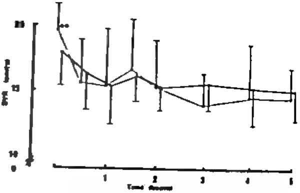

Figure 2. Calculated systemic vascular resistance (SVR) before (C) and following oral hydralazine (p<0.01).

o———o first invasive study
•———• second invasive study

DISCUSSION

A reduction in the systemic vascular resistance, i.e. afterload reduction, usually means that the failing heart can produce a higher SV (Cohn & Franciosa 1977). This beneficial effect has been shown for several different arterial vasodilators (Aronow *et al* 1979, Davis *et al* 1979, Weber *et al* 1980). However most knowledge is based upon acute or short term studies. Whether the initial hemodynamic response remains when the drug is adminstrered as maintenance therapy or not is less well known.

Thus, regarding prazosin it has been claimed that the acute response diminishes when the drug is administered chronically (Packer *et al* 1979). This strengthens the need for studies including long term treatment and repeated invasive investigations.

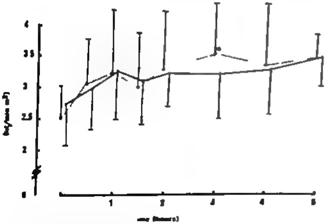

Figure 1. Cardiac index (CI) before (C) and following oral hydralazine (p<0.05)

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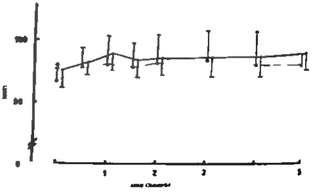

Figure 3. Stroke volume (SV) before (C) and following oral hydralazine (p<0.05)

•———• first invasive study
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HYDRALAZINE VERSUS PLACEBO IN CHF – PRELIMINARY RESULTS FROM A MULTICENTER LONG TERM STUDY IN SWEDEN

Thor-Björn Conradson

Today we are generally not ready to accept a new therapeutic approach until controlled studies have proven its efficacy. This is something that should have been applied on drugs like digitalis and diuretics too, but they were "lucky enough" to be introduced when medical therapy still was more belief than knowledge.

The vasodilators have been introduced as a new therapeutic tool in congestive heart failure (CHF) mainly during the last decade, i.e. during the era of respect for controlled studies. In spite of this, the huge literature on vasodilators in CHF mainly deals with open, short-term studies and only limited information is available about the long-term effects. To further study the role of hydralazine in the treatment of CHF a "four-hospital study" was designed including the hospitals of Falun, Huddinge, Lund and Skövde (Sweden). Some preliminary results from the first 6-months follow-up will be presented here.

DESIGN OF THE STUDY

For inclusion all patients should have symptoms of CHF corresponding to NYHA Class III. Furthermore the patients should be *optimally digitalized* and treated with any diuretic corresponding to 80 mg furosemide or more. Patients fulfilling these criteria were included irrespective of the etiology of CHF. Altogether 62 patients were enrolled.

The patients were hospitalized during the first days, i.e. during the dose-titration period. Subsequently they were, if possible, treated as out-patients. At month 0, 1, 2, 4 and 6 they underwent a physical examination including symptom evaluation. Routine blood chemistry was made at month 0 and 6. At month 0, 2 and 6 they were exercised on a bicycle ergometer.

DOSE TITRATION

The patients were randomly added hydralazine or placebo in a double-blind manner. The following dose-titration procedure was used:

Day 1 – Dose 1 25 mg
Day 1 – Dose 2 50 mg
Day 1 – Dose 3 75 mg
Day 2 + 75 mg t.i.d.

Intolerable side-effects, a drop of systolic pressure below 95 mm Hg or an increase in heart rate above 110 beat/min were the criteria for dose reduction. Following these criteria the average daily dose of hydralazine achieved was: 150 mg (range: 75–225 mg).

COMPARISON OF THE GROUPS

At month 0 there was no difference between the groups with respect to age, sex, etiology and duration of CHF, weight, respiratory rate and blood chemistry. Systolic blood pressure was also equal in the two groups but heart rate was somewhat, however not significantly higher in the hydralazine group.

EVALUATION OF SYMPTOMS

The symptom classification was done in two ways:

1. according to the NYHA-classification (Figure 1)
2. by use of a visual analogue scale, where the patient as well as the physician was asked to rate the severity of the patient's heart failure (Table 1).

At month 0 all patients by definition were NYHA III. Using the visual analogue scale there was, both according to the physicians and the patients' rating, no difference between the two groups at month 0. However, in the hydralazine group, the patients were significantly more diseased according to the investigators' rating compared to the patients' own rating.

*Coordinator Medical Department, Kärnsjukhuset, Skövde, Sweden

**Participating centres: Central Hospital, Falun (Ahlmark G and Saetre H), University Hospital, Huddinge (Nyquist O), University Hospital Lund (Persson S) and Kärnsjukhuset, Skövde (Conradson T-B and Ryden L).

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DISCUSSION

Cohn

I think these are very interesting data and I suspect that you are a bit disappointed in the relative lack of dramatic improvement in these patients. We participated in a study organized by CIBA-GEIGY a few years ago in the U.S.A. in which five centres participated in a hydralazine trial and the results were even more disappointing, i.e. after analysis of the data there were no differences between the placebo and the hydralazine treated group in any parameter that we looked at including exercise tolerance. It is hard to know whether hydralazine alone is just not a very good drug or whether the design of the study was inadequate. You are going further. Our study was terminated at six months. Your data so far suggest that there may be benefits to be demonstrated later on. But there are certain problems in the design of such studies. One of the things we became aware of was that maximal exercise testing in these patients is very difficult to achieve and it is certainly not achieved to the same degree in different laboratories and by different people. In our new V.A. cooperative study we are monitoring oxygen consumption and R.Q.s during exercise. Everybody is going to be pushed to a rise in R.Q. and to a maximum plateau of oxygen consumption. The other thing is that when you look at the acute hemodynamic response to these drugs during exercise one is impressed that the benefits at sub-maximal exercise appear to be clear whereas there is very little benefit at maximal exercise. This suggests that perhaps a better way to assess the response would be a sub-maximal test. At this point I think you would have to conclude that you are not absolutely convinced that hydralazine is going to turn out to be better than placebo in these patients.

Conradson

Dr Chatterjee could you comment on your side effects and dose levels and ours?

Chatterjee

We found that most side effects occured at the beginning of the treatment. Interestingly, the less sick the patient the more side effects were observed. The patients who are virtually moribund class IV or class IV++ tend to have less side effects. About 90 % of our patients responded to a 300 mg daily dose while only about 25 % patients responded to less than 200 mg.

FOLLOW UP

The placebo patients as well as the hydralazine patients improved symptomatically (Table IV). At month 6 still 35 % of the remaining placebo patients were classified as NYHA II. At the 6 month follow up 50 % of the hydralazine patients were symptomatically improved but that looks more promising is the tendency of a continous improvement in the hydralazine group while the patients in the placebo group are stable or maybe even start to decline (see Figure 1).

Symptom evaluation using the visual analogue scale showed a highly significant improvement in the hydralazine group according to the investigators rating. Also the placebo patients improved however not significantly. In the patients' self-rating there was an improvement in both groups, more pronounced in the placebo group than in the hydralazine group (Table V).

EXERCISE TEST

At month 6 a small but significant increase in the maximum exercise capacity was noted in the hydralazine group while the working capacity was unchanged in the placebo group (Table II). Heart rate measured with the patients in different body positions and exercising on different work load levels showed a non-significant trend towards lower values at month 6 compared to month 0.

CONCLUSIONS

The preliminary observations seem to show a positive trend for the hydralazine group with respect to

- symptomatic improvement which so far seems to be progressive
- a small but clear increase in exercise tolerance
- no signs of increased mortality
- but, a lot of side-effects was seen during the dose titration period, suggesting that longer dose-titration periods should be used.

Another interesting finding is the symptomatic improvement in the placebo group. Placebo-effects were of course expected but we had not expected that 35 % of the placebo patients still at month 6 would report

Table IV. NYHA-classification

Placebo group	*Month*	0	2	4	6
	I				
	II		9	9	7
	III	30	15	[illegible]	11
	IV				2
Hydralazine					
	I		1	1	1
	II		7	9	9
	III	32	15	12	9
	IV				1

Table V. Visual analogue scale at month 0 and month 6. H-0 and H-6 Median of the hydralazine group at month 0 and 6 respectively.
P-0 and P-6 Median of the placebo group at month 0 and 6 respectively.

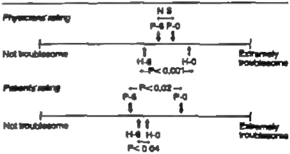

Table III. Drop-outs

Time	*Placebo*		*Hydralazine*	
Week 1	1	palpitation	1	fever
			2	headache
Month 1	1	dizziness	2	worsening of heart failure
	1	worsening of heart failure	1	AMI, non-fatal
			1	AMI, fatal
Month 2	1	not cooperable	2	worsening of heart failure
	1	AMI, fatal		
	1	sudden death		
Month 4	1	died during sleep at home	1	died during sleep at home
	1	died in progressive heart failure		
Month 6	1	AMI, fatal	1	AMI, fatal
	1	died in progressive heart failure	1	died in progressive heart failure

EXERCISE TEST

The exercise test was performed on a bicycle ergometer starting at 10 W and with a step-wise increase of 10 W/min until symptom limited maximum was reached

At month 0 the maximum load was somewhat higher in the placebo group and there was a tendency for higher heart rate in the hydralazine group (Table II).

SIDE EFFECTS

In the hydralazine group 16/32 patients experienced side-effects during the dose titration highly suspected to be drug related

12/16 continued treatment after reduction of the dose.

1/16 continued treatment without dose-reduction, in spite of the side-effects and 3/16 refused further treatment

In the placebo-group only 3/30 reported side-effects during the dose titration Of these patients, 1 continued treatment after dose reduction 1 continued treatment in spite of the side-effects and 1 refused further treatment.

The high rate of side-effects in the hydralazine group probably to some extent reflects the rapid titration schedule but still there is a marked difference in the

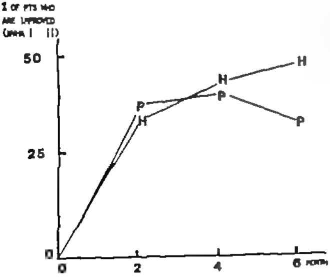

Figure 1 Percentage of improved patients of those remaining in the study at month 2, 4 and 6 (P= placebo patients, H= hydralazine patients).

Table I Visual analogue scale. H-O Median of the hydralazine group a month 0
P-O Median of the placebo group at month 0.

Question to the physician	"What is your overall clinical assessment of the patient's chronic heart failure?"
Question to the patient	"How do you experience your heart failure symptoms"?

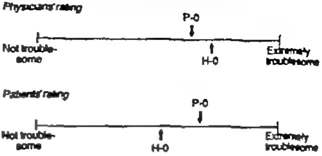

Table II Exercise test month 0 and month 6 Medium values

Placebo	*Month 0*	*Month 6*	
Max.load	60 W	60 W	n s
HR-lying	76	70	n s
HR sitting	88	82	n s
HR 30 W	103	91	n s
HR 50 W	110	105	n s
Hydralazine			
Max.load	50 W	60 W	$p < 0.015$
HR-lying	[illegible]	81	n s
HR sitting	91	85	n s
HR 30 W	105	102	n s
HR 50 W	121	112	n s

tolerability of hydralazine in our study compared to some other reports.

DROP-OUTS

There were 10 drop-outs in the placebo group and 12 in the hydralazine group (Table III) Of "major events" 6 died a "cardiac death" in the placebo group and 4 in the hydralazine group. If non-fatal AMI and worsening of CHF also are included as "major events there will be 7/10 in the placebo group and 9/12 in the hydralazine group

FOLLOW UP

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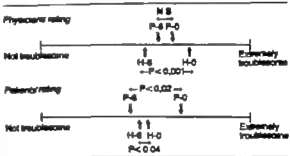

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	1	died in progressive heart failure	1	died in progressive heart failure

improvement. This finding indicates that even a marked improvement in an open study includes a great proportion of placebo influence and further strengthens the need for controlled studies.

DISCUSSION

Rydén

I would like to discuss the hydralazine dosage. We heard that some patients seem to need very high amounts of the drug and others do quite well on fairly low amounts. I wonder if this is a matter of response to hydralazine or if it is just something which reflects a varying metabolism in patients with different degree of CHF

Conradson

I think this fits into what Dr Chatterjee told us. Our patients were much less sick than the patients he told us about. Thus, they respond to lower doses than his patients.

Rydén

Dr Chatterjee, have you studied your patients as regards acetylating capacity in the relation to the need of drug and degree of CHF?

Chatterjee

We have. In fact all patients who needed a very large dose, say 800–1200 mg/day were fast acetylators. However there are many patients who are fast acetylators who also respond to a smaller dose. The second point is that we have seen many patients who did not respond initially at a given dose who with continued administration, 48–72 hours, responded in terms of an increase in CO

Rydén

An interesting thing is that gynecologists are using hydralazine for treatment of hypertension in pregnancy. The pregnant women seem to stand high doses of Apresoline. We are not used to see our patients being able to take such doses without side-effects. It might be a large difference in the metabolism or absorption of hydralazine in different types of patients which could be an explanation.

CAPTOPRIL – AN ORAL ANGIOTENSIN-CONVERTING ENZYME INHIBITOR IN CHF

Kanu Chatterjee, Jean-Lucien Rouleau and William W. Parmley

INTRODUCTION

One of the major pathophysiologic consequences of myocardial failure is a reduction in systemic output. In order to maintain arterial pressure, there is compensatory increase in systemic vascular resistance (Chatterjee & Parmley 1977, Parmley & Chatterjee 1978). This increase in systemic vascular resistance, however also leads to an increase in the left ventricular outflow resistance which can further reduce cardiac output (CO) (Chatterjee & Parmley 1977, Cohn 1973, Parmley & Chatterjee 1978). Thus, a vicious cycle may develop that will ultimately lead to a lower steady state level with a reduced CO and an inappropriately high systemic vascular resistance. That the compensatory increase in systemic vascular resistance to maintain arterial pressure in patients with heart failure (CHF) may sometimes be inappropriate and excessive is evident from the fact that many vasodilator agents can produce a marked decrease in systemic vascular resistance, a comparable increase in CO and little or no change in arterial pressure (Chatterjee *et al.* 1976). Thus, the increase in systemic vascular resistance in such circumstances must be considered inappropriate and is not required to maintain arterial pressure, but does decrease CO. This suggests that this compensatory increase in systemic vascular resistance is not necessarily an entirely beneficial physiologic effect. The mechanism by which systemic vascular resistance is elevated in patients with CHF associated with low CO is incompletely understood. It is likely that several neural, humoral, or neurohumoral factors might be operative (Zelis *et al.* 1970, Zelis *et al.* 1979). Enhanced activity of the sympathetic nervous system and increased circulating catecholamines have been thought to contribute to peripheral arteriolar vasoconstriction. In the presence of CHF there may also be increased stiffness of the arteriolar wall due to local retention of sodium and water. It has also been suggested that in patients with CHF associated with low CO, the renin angiotensin system may be stimulated and increased levels of angiotensin might contribute to an increased systemic vascular resistance (Brown *et al.* 1977, Genest *et al.* 1968, Johnsson *et al.* 1968, Merrill *et al.* 1946, Watkins *et al.* 1972). Attenuation or inhibition of the effects of angiotensin, therefore, would be expected to reduce systemic vascular resistance and thereby improve cardiac performance. Indeed, with the use of a specific competitive angiotensin antagonist, saralasin, increase in CO along with a decrease in systemic vascular resistance has been reported in some patients with chronic CHF (Gavras *et al.* 1977). Furthermore, decreased formation of angiotensin-II, the active vasoconstrictor following administration of an angiotensin-converting enzyme inhibitor, teprotide, has been shown to cause a significant reduction in systemic vascular resistance and improvement in left ventricular function in patients with CHF (Curtiss *et al.* 1979, Gavras *et al.* 1979). Teprotide or saralsin, however, need to be administered intravenously and, therefore, have only limited applications for the long term management of patients with chronic CHF. Captopril, an oral angiotensin-converting enzyme inhibitor which has the similar potential to cause attenuation or inhibition of the effects of vasoconstrictor angiotensin-II is more suitable for the long term management of patients with chronic CHF.

HEMODYNAMIC EFFECTS OF CAPTOPRIL IN CHRONIC HEART FAILURE

In patients with chronic CHF refractory to conventional therapy, captopril produces beneficial hemodynamic and clinical response (Ader *et al.* 1980, Davis *et al.* 1979, Dzau *et al.* 1980, Levine *et al.* 1980, Turini *et al.* 1979). The hemodynamic effects of oral captopril (25 mg) in a group of patients with chronic CHF are

From the University of California, San Francisco, California, U.S.A.

Table 1. Hemodynamic effects of oral captopril (25 mg) in patients with CHF

	Control	Captopril	p<
Heart rate (beats/min)	78±15	67±15	0.05
Mean arterial pressure (mm Hg)	92±19	71±20	0.05
Pulmonary capillary wedge pressure (mm Hg)	29±8	15±6	0.05
Mean pulmonary artery pressure (mm Hg)	41±9	28±6	0.05
Mean right atrial pressure (mm Hg)	11±4	8±4	0.05
Cardiac output (L/min)	3.9±1.7	5.1±1.8	0.05
Systemic vascular resistance (dynes sec cm $^{-5}$)	1798±653	1066±362	0.05
Stroke work index (g m/m^2)	31±11	39±8	0.05

summarized in Table 1 (Adler *et al.* 1980). Within a half hour of oral administration CO increased significantly and remained elevated for approximately seven hours. In most patients the maximum increase in CO occurred usually between two and four hours. Concomitant with the increase in CO pulmonary capillary wedge pressure fell, and remained at a lower level compared to control for approximately seven hours. An increase in CO along with a fall in PCWP indicated improved cardiac performance. Systemic vascular resistance and pulmonary vascular resistance also decreased significantly. In most patients there was a marked increase in stroke volume (SV) and stroke work index. The average increase in SV was 49 % and in stroke work index 26 %. There was only a modest decrease in arterial pressure in most patients; however in two patients arterial pressure fell markedly. At the time of maximum decrease in arterial pressure, heart rate also decreased. The magnitude of decrease in heart rate in general was small, however in occasional patients, marked bradycardia was observed.

The hemodynamic response to 50 and 100 mg doses of captopril was compared in the same patients who received 25 mg doses of captopril. These responses are illustrated in Figure 1. Cardiac output increased by similar magnitude following each dose of captopril. Left ventricular filling pressure fell by an average of 46 % following the 25 mg dose, and the fall in left ventricular filling pressure after 50 or 100 mg was also similar. The magnitude of decrease in systemic vascular resistance was −41 %, mean arterial pres[sure] −23 %, heart rate −14 %, and right atrial pres[sure] −27 % following the 25 mg dose and was al[most] identical to that following the 50 or 100 mg do[ses]. Although in this study the hemodynamic respo[nses] after 50 and 100 mg doses of captopril were no be[tter] than those after 25 mg, other investigators have [re]ported the necessity of using a larger dose to prod[uce] optimal hemodynamic responses (Davis *et al.* 1[979], Tunni *et al.* 1979, Dzau *et al.* 1980, Levine *et al.* 19[80]).

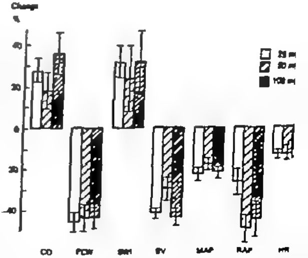

Figure 1. Magnitude of changes in cardiac output (CO), p[ul]monary capillary wedge pressure (PCW), stroke work in[dex] (SWI), systemic vascular resistance (SVR), mean arte[rial] pressure (MAP), right atrial pressure (RAP) and heart r[ate] (HR) after 25, 50 and 100 mg of captopril (Ader *et al.* 19[80])

Captopril-induced hemodynamic changes observed in our study were qualitatively and quantitatively similar to those reported in other investigations (Davis *et al* 1979 Turini *et al.* 1979 Dzau *et al* 1980 Levine *et al* 1980) The magnitude of increase in CO in these studies has ranged from 15 to 38 % and the fall in pulmonary capillary wedge pressure from 25 to 46 % Contrary to the results in our study relative bradycardia was infrequently observed in other investigations However some decrease in arterial pressure was a universal finding.

The mechanism for the improvement in cardiac performance with captopril in patients with CHF is not entirely clear As there was a consistent decrease in systemic vascular resistance associated with an increase in CO and SV and a significant correlation was found between the relative changes in systemic vascular resistance and CO (Figure 2), a reduction in left ventricular outflow resistance must play a role. The reduction of systemic vascular resistance during captopril therapy however does not appear to be entirely due to the attenuation of the effects of angiotensin-II (Collier *et al* 1973 Williams & Hollenberg 1977) There was only a general correlation between the magnitude of fall in systemic vascular resistance and the initial level of plasma renin activity (Figure 3) Furthermore, no correlation was found between the initial level of systemic vascular resistance and the control plasma renin activity This poor correlation between systemic vascular resistance and plasma renin activity indicated that the reduction of systemic vascular resistance by captopril is not entirely due to a decrease in the levels of circulating angiotensin-II. It has been demonstrated that captopril inhibits the degradation of bradykinin (Engel *et al* 1972 Ferreira 1965) and, therefore, kinin-induced vasodilatation

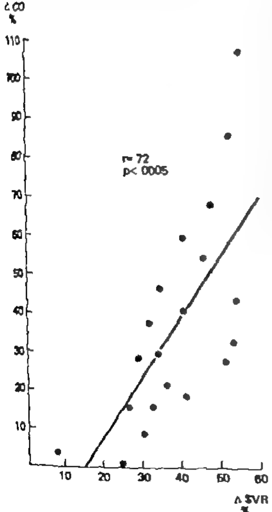

Figure 2 Correlation between changes in CO (Δ CO) and systemic vascular resistance (Δ SVR) following captopril in patients with CHF

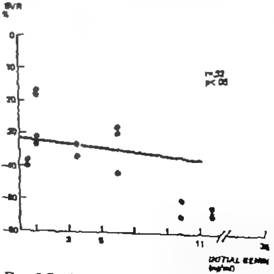

Figure 3 Correlation between the initial plasma renin activity and the magnitude of changes in systemic vascular resistance (Δ SVR)

Table II Changes in coronary hemodynamics and myocardial oxygen consumption following captopril in chronic ischemic heart failure.

	Control	*Captopril*	*p*
Heart rate x arterial pressure (mm Hg/min x 10^{-3})	10.8±2.1	8.0±2.1	0.001
Coronary sinus flow (ml/min)	64±22	57±26	0.02
Myocardial oxygen consumption (ml/min x 10^{-2})	8.2±2.8	6.7±3.2	0.02
% *lactate extraction*	38±15.7	38±19.7	NS

NS = No significance

with the consequent reduction of systemic vascular resistance *remains a possibility. Decreased sympathetic* activity following captopril therapy may also be contributory in reducing systemic vascular resistance. *Recent investigations have indicated that following* administration of angiotensin-converting enzyme inhibitors, there may be a fall in the level of circulating catecholamines (Curtiss *et al.* 1979, Turini *et al.* 1979).

A substantial decrease in systemic and pulmonary venous pressures with captopril is another consistent finding in patients with CHF. Evaluation of changes in the peripheral venous tone with the use of plethysmography has indicated that there may be a significant decrease in venous tone following administration *of captopril in patients with chronic CHF. The* mechanism of this venodilatory effect of captopril however, remains unclear. It is generally accepted that *angiotensin causes constriction of resistance or pre*capillary vessels while the veins or the capacitance vessels are relatively insensitive to the direct constricting effect of angiotensin (Cohn 1966, *Gross & Bock* 1962, Haddy *et al.* 1962, Rose *et al.* 1962, DePasquale & Burch 1963[a, b]). It is likely, therefore, that the venodilatory effect of captopril is an *indirect one. A reduction* in aldosterone level that has been observed following captopril therapy *may* be contributory in reducing peripheral venous tone. The decreased level of circulating catecholamines consequent upon the improvement in left ventricular function may also play a role in reducing systemic and pulmonary venous pressures. The reduction *in* catecholamine level might also explain the relative bradycardia that is observed in some patients following captopril therapy. Irrespective of the underlying mechanism, a reduction in heart rate with a concomitant decrease in arterial pressure and pulmonary capillary wedge pressure is likely to be beneficial in terms of metabolic costs, particularly in patients with ischemic heart disease.

INFLUENCE OF CAPTOPRIL THERAPY ON CORONARY HEMODYNAMICS AND MYOCARDIAL OXYGEN CONSUMPTION

In ten patients with chronic ischemic heart failure, changes in coronary sinus flow, myocardial oxygen *extraction, and oxygen consumption along with trans*myocardial lactate extraction were evaluated before and after captopril therapy (Table II). In all patients *there was a reduction in peak systolic pressure.* The heart rate also decreased in the majority of patients. The product of the peak systolic pressure and heart rate, an index of myocardial oxygen demand, therefore, decreased in all patients. The average decrease in the rate pressure product was 26 %. Concomitant *with the reduction in the rate pressure product,* there was also a decrease in coronary sinus flow and in calculated myocardial oxygen consumption. The average decrease *in myocardial oxygen consumption in these* patients was 25 %. There was no evidence of enhancement *of myocardial ischemia,* as there was *no change* in transmyocardial lactate extraction. *The improve*ment in cardiac performance was evident in these patients from an increase in CO and a fall in pulmonary capillary wedge *pressure following captopril therapy.* Thus, improved left ventricular function with captopril was not associated with any increase in the metabolic cost. *These findings suggest that the decrease in the*

determinants of myocardial oxygen demand and oxygen consumption with captopril may be particularly beneficial in patients with chronic ischemic heart failure.

HEMODYNAMIC AND CLINICAL RESPONSE TO LONG TERM CAPTOPRIL THERAPY

Before long term therapy with any vasodilator agent is advocated, it is desirable to establish the sustained hemodynamic and clinical response of the vasodilator agents during maintenance therapy. Changes in the clinical status and hemodynamics were evaluated in seven patients with severe refractory CHF at the end of eight weeks of maintenance captopril therapy (Ader et al 1980). Five of these seven patients were in New York Heart Association Class III and the remaining two were in Class IV before the initiation of therapy. Six of the seven patients on maintenance therapy had improvement by one clinical class, only one patient showed no clinical improvement (Figure 4). Exercise duration in these patients also increased by an average of 48 %. These clinical observations indicate that sustained improvement in the symptoms of CHF and increased effort tolerance can occur in some patients with chronic CHF receiving long term captopril therapy. The hemodynamic effects of captopril at the beginning of the therapy and after eight weeks of maintenance therapy in these seven patients are summarized in Table III. After the initiation of therapy mean arterial pressure decreased by 21 % and at eight weeks

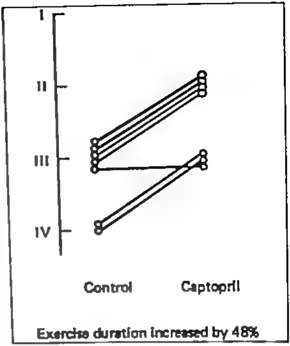

Figure 4. Changes in the clinical status following eight weeks of maintenance captopril therapy.

Table III. Hemodynamic response at the initiation and after eight weeks of maintenance captopril therapy in seven patients with chronic CHF

	Control	Immediate response	Eight weeks	Control vs. immediate response	Control vs. eight weeks
Heart rate (beats/min)	78±16	67±15	73±17	p<0.05	p<0.05
Mean arterial pressure (mm Hg)	89±16	70±15	68±9	p<0.05	p<0.05
Mean pulmonary capillary wedge pressure (mm Hg)	29±9	16±4	13±7	p<0.05	p<0.05
Mean pulmonary artery pressure (mm Hg)	40±10	28±7	27±14	p<0 [illegible]	p<0.05
Mean right atrial pressure (mm Hg)	12±3	9±3	5±2	p<0.05	p<0.05
Cardiac output (L/min)	3.54±1.66	4.38±1.30	5.09±1.54	p<0.05	p<0.05
Stroke volume (ml/beat)	46±20	68±22	72±26	p<0.05	p<0.05
Stroke work index (g-m/m^2)	28±12	36±8	35±7	NS	NS
Systemic vascular resistance (dynes sec cm^{-5})	1933±753	1175±384	1084±327	p<0.05	p<0.05

a similar decrease of arterial pressure was observed. Initially captopril produced an increase of CO by 24 % but at eight weeks of maintenance therapy the average increase in CO (41 %) was significantly higher. The changes in SV and pulmonary capillary wedge pressure at the beginning of the treatment and after eight weeks of captopril therapy are illustrated in Figure 5. In all seven patients SV increased initially and this increase was maintained at eight weeks. Similarly pulmonary capillary wedge pressure decreased in all patients initially and remained low at the time of restudy. The persistent increase in SV along with the sustained decrease in pulmonary capillary wedge pressure indicated a sustained improvement in left ventricular function in these patients. Sustained improvement in the hemodynamic and clinical status of patients with chronic CHF have been reported previously with continued long term captopril therapy. An increase in left ventricular ejection fraction determined by gated blood pool scintigraphy was also observed following six months of captopril therapy. A reduction of left ventricular end-diastolic diameter by echocardiography may also occur in some patients. These preliminary investigations suggest that chronic oral captopril therapy may provide sustained beneficial effects on cardiac dynamics in patients with chronic CHF.

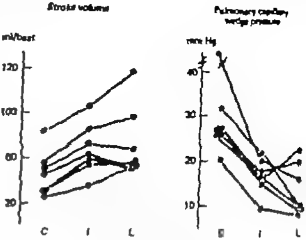

Figure 5. Changes in SV and pulmonary capillary wedge pressure after initiation (I) and eight weeks of captopril treatment (L) compared with control (C) in seven patients with chronic CHF. Increased SV and decreased pulmonary capillary wedge pressure observed initially were sustained at eight weeks (Ader et al. 1980).

ADVERSE EFFECTS

It appears that captopril is well tolerated by the majority of patients with chronic CHF. In some patients, however, marked hypotension and bradycardia may occur at the initiation of treatment. Skin rash may develop in occasional patients and discontinuation of therapy may be required. Immune complex membranous glomerulonephritis has been suspected in some patients receiving captopril therapy although this complication did not occur in our patients.

SUMMARY

Captopril, an oral angiotensin-converting enzyme inhibitor, increases CO, SV and stroke work and decreases pulmonary and systemic venous pressures in patients with CHF. These beneficial hemodynamic effects persist during maintenance captopril therapy. Myocardial oxygen consumption tends to decrease, along with a decrease in the determinants of myocardial oxygen demand. As improvement in left ventricular function occurs with a decreased metabolic cost, captopril has the potential to be a valuable addition to vasodilator therapy of CHF.

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DISCUSSION

Rydén.

My impression is that at present there is a considerable interest for this drug. Do you think that it might be an alternative to hydralazine and nitrates in combination.

Chatterjee.

I do not think so. We have just completed a study comparing the haemodynamic response of single doses of hydralazine, prazosin and captopril. We found that the initial response with captopril, prazosin and hydralazine are very similar but with continued therapy the response to captopril is much less compared to that with hydralazine. Continued therapy with prazosin in our experience results in markedly accentuated haemodynamic effects.

CLOSING REMARKS

Lars Rydén

My impression is that the concept of vasodilating drugs stands on a safe physiological ground and that it has been definitely proven to give beneficial effects in the acute situation. One problem is the demand for continuous patient monitoring. It feels necessary to have certain information on filling pressures and CO prior to the choice of one of several drugs available and it seems still to be difficult to titrate the correct dose without these tools. However bedside techniques for pulmonary artery catheterization are well developed and at least at rest it seems accurate to use thermal dilution for determination of CO. These methods should be possible to use in intensive care units even in small hospitals.

The concept of vasodilation on chronic terms seems to me worthwhile spreading out at least in patients with refractory CHF. In these patients hydralazine and hydralazine combined with nitrates could be used without large difficulties. Ordinary supervision is enough for dose titration in the common case. Whether prazosin is useful or not seems to me at present controversial. It represents a convenient drug including effects both on the venous and arterial side. In particular patients it seems to have proven effect but in my opinion many disappointing experiences have also been published. Captopril might become an interesting alternative. In chronic treatment there remains as you have heard lots to be done. Further studies of the hormonal influence, peripheral circulatory state, organ perfusion has to be done. An interesting field to study is the combined use of β-stimulators and vasodilating drugs.

There is a need for more controlled studies of the type going on at the four Swedish hospitals. The observation that placebo patients at least subjectively improved must make us very careful when interpreting data from open studies. I also think that observations made only at rest and in supine exercise has to be abandoned and work in the upright position could give us valuable information in the future regarding the definite role of vasodilating drugs in CHF.

Acta Medica Scandinavica

Supplementum 656

Diabetes–Research and Clinical Practice

Proceedings of a Symposium in Malmö Sweden, May 30–31 1980

Edited by Lars Olof Almér

Distributed by The Almqvist & Wiksell Periodical Company Stockholm, Sweden

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Subscription, Distribution and Advertising

The Almqvist & Wiksell Periodical Company
Gamla Brogatan 26 Box 62
S-101 20 Stockholm 1 Sweden

Printers

Almqvist & Wiksell
S-751 [illegible] Uppsala, Sweden

ISSN 0365-463X

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I am most grateful to all my collaborators at the University of Lund at the Departments of Medicine in Malmö as well as in Lund. Without the kind help and planning by Professor Bertil Hood, Malmö and Associate Professor Bengt Scherstén, Lund it would have been impossible to arrange this meeting.

Very generous contributions from NOVO INDISTRI AB made this symposium possible and all of us—organizers as well as participants—would like to express our gratitude to NOVO for the support.

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Acta Med Scand Suppl

B-cell Secretion in Non-diabetics and Insulin-dependent Diabetics

Lise G. Heding, Johnny Ludvigsson and Teresa Kasperska-Czyzykowa

From Novo Research Institute, DK-2880 Bagsvaerd, Department of Paediatrics, University Hospital, S-58185 Linköping, and Department of Gastroenterology and Metabolic Diseases, Medical Academy in Warsaw, ul. Lindleya 4, P-02-005 Warsaw

In the pancreas the islet tissue amounts to about 1% by weight and of this about 80% of the cells in the islets are B-cells. Thus 100 g pancreas ~1 g islets ~800 mg B-cells containing about 15 mg of insulin. The biosynthesis of proinsulin or rather preproinsulin takes place at the rough endoplasmatic reticulum and the enzymatic conversion of proinsulin occurs in the Golgi apparatus.

The conversion seems to be related to the formation of pregranula. After the conversion of proinsulin to insulin and C-peptide, the insulin is stored together with Zn in the crystal-like masses while surrounded by C peptide in the soluble state. Upon stimulation of the B-cell, the granula are secreted directly into the blood. The enzymatic conversion of proinsulin to insulin and C-peptide is not complete in humans and the B-cell contains approx. 5% of non-converted proinsulin and intermediates. It is not known whether proinsulin is stored together with insulin and C-peptide in the granula and secreted together with these or by other routes (4).

Upon enzymatic conversion proinsulin is cleaved into insulin and C-peptide loosing at the same time two pairs of basic amino acids. The C peptide itself does not seem to have any biological activity whatsoever—apart from ensuring the correct folding of the complicated insulin molecule. However its secretion into the blood which seems to be a waste on the part of nature gives us a unique tool in diabetes research with which to investigate the natural course of the B-cell in insulin-dependent diabetes mellitus (IDDM) after exogenous insulin treatment has been started.

The molar ratio between C-peptide and insulin is 1:1 and as mentioned the B-cells contain about 5% proinsulin. At the moment of secretion the ratio between the three B-cell secretory products is approximately 100:100:5 (Fig. 1). In peripheral blood the ratio is different due to the different metabolic clearances of the three products. Thus about 50% of the insulin is taken up by a single liver passage, whereas C-peptide and proinsulin pass this organ with only minor changes taking place.

Methods for determining insulin C-peptide and proinsulin

Since all three B-cell secretory products are present in the plasma, three RIA's are needed. However the fundamental problem is that a RIA for C-peptide will determine proinsulin as well, and that the RIA for insulin will likewise co-determine proinsulin.

It is therefore necessary to perform a separation and remove proinsulin before determining C-peptide. This is done by a so-called solid-phase method, where a suspension of insulin antibodies, co-valently bound to Sepharose particles, is mixed with the serum (Fig. 2). All molecules with an insulin moiety—including proinsulin are then bound to these particles and then easily removed by centrifugation. C-peptide is then determined in a usual RIA (1).

The insulin RIA was first described by Yalow and Berson in 1960 and is easy to establish. Unfortunately most insulin RIA's also measure proinsulin to varying degrees. In the RIA used in this investigation (Fig. 3), proinsulin reacts about 67% on a molar basis as compared to the insulin. This means, in other words, that if serum contains proinsulin in a ratio of, e.g., 50:50 then the RIA will grossly over-estimate the insulin.

Hence use of the term IRI (immunoreactive insulin) is absolutely necessary in order to avoid confusion and if insulin is to be determined, proinsulin has to be subtracted.

Proinsulin is determined bound to the Sepharose-AIS particles where its C-peptide moiety is still free and active (2).

Acta Med Scand, Suppl. 656: 5–9, 1981

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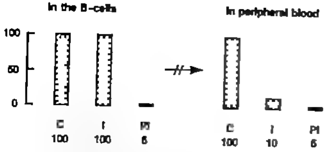

Fig 1 Molar ratios between C-peptide insulin and proinsulin in B-cells and peripheral blood

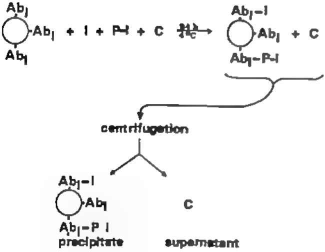

Fig 2 Schematic diagram showing the separation of proinsulin from C-peptide prior to RIA.

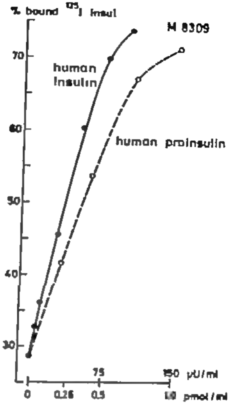

Fig 3 Human proinsulin reactivity in the insulin RIA

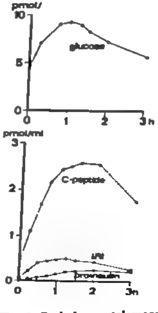

Fig 4 Oral glucose tolerance test (1 75 g/kg) in 12 non-diabetics.

The standard curve for proinsulin is extremely sensitive which is necessary as the proinsulin content in plasma in fasting non-diabetics is in the order of 0 01 pmol/ml

Non-diabetics

Fig. 4 shows an oral glucose tolerance (1 75 g/kg) test in 12 control persons The upper curve shows the usual glucose profiles and below C peptide IRI and proinsulin There is a fall between C-peptide and IRI between 2 and 3 h whereas proinsulin is unchanged Thus the concentration of proinsulin 3 h after ingestion of 100 g of glucose is very high just about the same concentration as the IRI

In order to determine insulin (and not IRI) C-peptide and proinsulin in control persons and to determine the true molar ratios between the three B-cell secretory products proinsulin was subtracted from IRI in order to obtain the correct value for insulin itself (3)

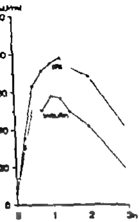

Fig 5 IRI and insulin curves following oral glucose in 12 non-diabetics.

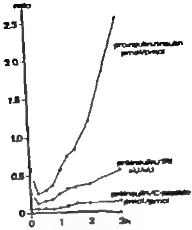

Fig 7 Molar ratios between proinsulin insulin, proinsulin IRI and proinsulin C-peptide following oral glucose in 12 non-diabetics.

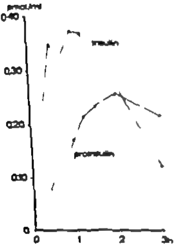

Fig 6 Insulin and proinsulin curves following oral glucose in 12 non-diabetics

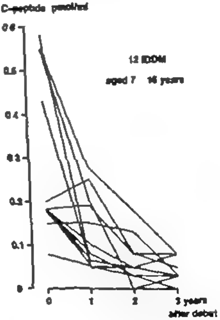

Fig 8 Fasting C-peptide in 12 insulin-dependent diabetic children until 3 years after the debut.

Theoretically 1 pmol of proinsulin should react as 1 pmol of insulin, because it contains one insulin moiety per molecule but, in practice proinsulin reacts somewhat less and in our assay 1 pmol of insulin reacts as 100 microunits of insulin.

Fig 5 shows the differences between the IRI curve and the insulin curve where the insulin curve has been made by subtracting the proinsulin values from the IRI values and as expected, there is a considerable difference betweeen the two curves already 30 min after the load was given. It is obvious that the IRI-assay over-estimates insulin grossly due to the presence of proinsulin.

Fig. 6 shows—depicted as pmol/ml—insulin and proinsulin; in the fasting state in normals about

Table I *IRI C-peptide and proinsulin in 22 newly diagnosed insulin dependent diabetic children and 85 non-diabetics (pmol/ml mean ± S D)*

	22 diabetic children	85 non-diabetics
IRI	0 070±0 042	0 055±0 024
C peptide	0.25 ±0 014	0 48 ±0 16
Proinsulin	0 039±0 052	0 017±0 011

Table II *IRI C peptide and proinsulin in 12 newly diagnosed juvenile diabetics (age 9–18 years)*

IRI (μU/ml)	C-peptide (pmol/ml)	Proinsulin (pmol/ml)
10	0 15	0.000
6	0 18	0 000
6	0 18	0 015
22	0.20	0 003
10	0 18	0 008
6	0 08	0 023
16	0.55	0 050
13	0 43	0 060
26	0 18	0 065
13	0.26	0.140
16	0 18	0.168
19	0.18	0 175

half as many molecules of proinsulin circulate as compared to insulin After 2 h the molar concentrations of insulin and proinsulin are similar then at 3 h there are more proinsulin molecules in plasma than there are insulin molecules

The molar ratios are shown in Fig 7 The ratio between proinsulin and insulin drops as expected, in the first phase of the stimulation of the B-cell whereafter the ratio gets higher indicating that more and more proinsulin is circulating as compared to insulin The second interesting observation is that the ratio between proinsulin and C-peptide which have approximately the same half-life in serum hardly shows any difference in the first hour indicating that the two products are secreted in the same ratio as they are present in plasma However between 1 to 2 and 3 h the ratio increases significantly from about 0 03 to about 0 12 which shows that proinsulin becomes more and more abundant as compared to C-peptide This could indicate that proinsulin is secreted in a higher proportion from the B-cell in the late phase of an oral glucose tolerance test

Diabetics

Table I shows the values of IRI C peptide and proinsulin in fasting non-diabetics and insulin-dependent diabetics The 22 diabetics all newly diagnosed diabetic children have a higher mean value of IRI at the time of onset than the control group

C peptide is clearly lower in the diabetics as compared to normals as could be expected meaning that the diabetic at the time of diagnosis has a lower endogenous insulin production as compared to the non-diabetics

Proinsulin in the newly diagnosed diabetics is more than twice as high as in the non-diabetics and this explains the higher value of IRI found in these patients Thus the diabetics do not usually have a higher mean insulin value but a higher IRI value From the figures in Table I it can be calculated that the percentage that proinsulin constitutes of C peptide in non-diabetics is about 4% whereas it is increased to 22 3% in the diabetics

Fig 8 shows fasting C peptide in diabetic children followed for approximately 3 years demonstrating a constant decline of endogenous secretion as measured by C peptide

In Table I it is shown that the mean value of proinsulin in diabetics is higher than in non-diabetics In Table II it can be seen that there is a wide scatter among the patients regarding their proinsulin values

The upper 6 patients have proinsulin values which all lie in the normal range whereas the lower 6 patients have very high proinsulin values their values are so high that practically all of their IRI is due to the activity of proinsulin Preliminary results indicated that the B-cell when it secretes proinsulin almost is exclusively in a very deteriorated state not capable of converting the proinsulin into C-peptide and insulin This problem is currently being investigated closer

Conclusion

The use of specific and sensitive C-peptide and proinsulin RIA s has extended our knowledge about B-cell secretion in health and diabetes. C-peptide measurements are the only way to monitor B-cell function in *insulin-dependent diabetics and thus* evaluate factors influencing the B-cell activity The finding of high amounts of non-converted proinsulin

in serum of newly diagnosed diabetics is intriguing and needs further investigation and comparison with non-diabetics in whom proinsulin also may rise to high levels following a heavy glucose load

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Table I *IRI C-peptide and proinsulin in 22 newly diagnosed insulin dependent diabetic children and 85 non-diabetics (pmol/ml mean ± S.D)*

	22 diabetic children	85 non-diabetics
IRI	0 070±0 042	0 055±0 024
C peptide	0 25 ±0 014	0 48 ±0 16
Proinsulin	0 039±0 052	0 017±0 011

Table II *IRI C peptide and proinsulin in 12 newly diagnosed juvenile diabetics (age 9–18 years)*

IRI (µU/ml)	C-peptide (pmol/ml)	Proinsulin (pmol/ml)
10	0.15	0.000
6	0 18	0 000
6	0 18	0 015
22	0.20	0 003
10	0 18	0 008
6	0 08	0 023
16	0.55	0 050
13	0.43	0.060
26	0 18	0 065
13	0.26	0 140
16	0 18	0.168
19	0.18	0 175

half as many molecules of proinsulin circulate as compared to insulin After 2 h the molar concentrations of insulin and proinsulin are similar then at 3 h there are more proinsulin molecules in plasma than there are insulin molecules

The molar ratios are shown in Fig. 7 The ratio between proinsulin and insulin drops as expected in the first phase of the stimulation of the B-cell whereafter the ratio gets higher indicating that more and more proinsulin is circulating as compared to insulin The second interesting observation is that the ratio between proinsulin and C peptide which have approximately the same half life in serum hardly shows any difference in the first hour indicating that the two products are secreted in the same ratio as they are present in plasma. However between 1 to 2 and 3 h the ratio increases significantly from about 0 03 to about 0 12 which shows that proinsulin becomes more and more abundant as compared to C peptide This could indicate that proinsulin is secreted in a higher proportion from the B-cell in the late phase of an oral glucose tolerance test

Diabetics

Table I shows the values of IRI C peptide and proinsulin in fasting non-diabetics and insulin-dependent diabetics The 22 diabetics all newly diagnosed diabetic children have a higher mean value of IRI at the time of onset than the control group

C peptide is clearly lower in the diabetics as compared to normals, as could be expected meaning that the diabetic at the time of diagnosis has a lower endogenous insulin production as compared to the non-diabetics

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Table I. *IRI, C-peptide and proinsulin in 22 newly diagnosed insulin dependent diabetic children and 85 non-diabetics (pmol/ml, mean ± S.D.)*

	22 diabetic children	85 non-diabetics
IRI	0.070±0.042	0.055±0.024
C peptide	0.15 ±0.014	0.48 ±0.16
Proinsulin	0.039±0.052	0.017±0.011

Table II. *IRI, C-peptide and proinsulin in 12 newly diagnosed juvenile diabetics (age 9–18 years)*

IRI (μU/ml)	C peptide (pmol/ml)	Proinsulin (pmol/ml)
10	0.15	0.000
6	0.18	0.000
6	0.18	0.015
22	0.20	0.003
10	0.18	0.008
6	0.08	0.023
18	0.55	0.050
13	0.43	0.060
26	0.18	0.065
13	0.26	0.140
16	0.18	0.168
19	0.18	0.175

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The use of specific and sensitive C peptide and proinsulin RIA's has extended our knowledge about B-cell secretion in health and diabetes. C peptide measurements are the only way to monitor B-cell function in insulin-dependent diabetics and thus evaluate factors influencing the B-cell activity. The finding of high amounts of non-converted proinsulin

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Acta Med Scand, Suppl. 656. 11–18, 1981

Effects of Sulfonylurea on the Secretion and Disposition of Insulin and C peptide

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ABSTRACT In an attempt to examine the influence of sulfonylurea on the secretion, disposition and effect of insulin, 9 diabetic patients were studied during three one-month medications with ( ) chlorpropamide ($t_{\frac{1}{2}}>33$ h) once daily (*b*) glipizide ($t_{\frac{1}{2}}$ 2–4 h) once daily and ( ) glipizide in divided dosage. The food intake of each patient was identical during each examination period. Blood concentrations of C-peptide, insulin, glucose, and drugs were determined before and after breakfast and lunch on the 4th day of each examination period. As expected, once-daily administration of glipizide led to higher after-breakfast concentrations of the drug than when the dose was divided. However the C-peptide changes following breakfast were similar both during these two treatments and also during chlorpropamide indicating that the amounts of insulin released from the pancreas were equivalent. In spite of this, glipizide once daily yielded 60–70% more insulin in systemic blood following breakfast than did the two other treatments. Reasonably this signifies that the hepatic extraction of insulin was reduced during once-daily glipizide, allowing more insulin to reach systemic circulation. In addition, this was found to promote more effective utilization of glucose following breakfast. Following lunch, the C-peptide release, the plasma insulin increase and the blood glucose reduction were greater when glipizide was given in divided dosage than when once-daily glipizide or chlorpropamide was employed. This occurred even though the after-lunch concentration of glipizide in systemic blood was lower rather than higher during divided than during once-daily administration. This supports the notion that the effect of orally administered sulfonylurea is determined not only by its concentration in systemic blood but also by its gastroenterohepatic appearance. Glipizide may offer greater therapeutic flexibility than chlorpropamide, but further studies are required to define the optimum choice and use of sulfonylureas.

Key ords sulfonylurea, C-peptide, insulin, extrapancreatic effects

Although sulfonylureas have been employed for more than 20 years, there is still no consensus as to how they maintain blood glucose reduction during long-term treatment Unquestionably sulfonylureas promote insulin release from the pancreatic B cells, but the correlation between their influence on plasma insulin and on blood glucose is poor (1) Sulfonylureas appear to have extrapancreatic effects, they can inhibit glucose release from the liver (2, 3) and they may influence the interactions between insulin and its receptors (4 5) In addition there is evidence to suggest that, although sulfonylureas stimulate the secretion of insulin they may impair its biosynthesis (6, 7) This would restrict the therapeutic effect of sulfonylureas, particularly if they are used so as to yield continuous exposure i.e. that the drug is present in body fluids 24 hours a day

In an attempt to examine these aspects the present study assessed the C-peptide insulin and glucose profiles in blood following breakfast and lunch in diabetics exposed to one-month treatments with (*a*) a long-lived sulfonylurea, chlorpropamide (*b*) a short-lived sulfonylurea, glipizide once daily and ( ) glipizide in divided dosage during monitoring of the drug concentrations in plasma.

MATERIAL AND METHODS

Subjects

Five females and four male patients with non-insulin-dependent diabetes mellitus were studied. Their mean age was 68 years (range 48–80) and the mean duration of the disease after diagnosis was 9.5 years (range 1–19). Their mean weight was 126% of ideal (range 89–154%). Six of

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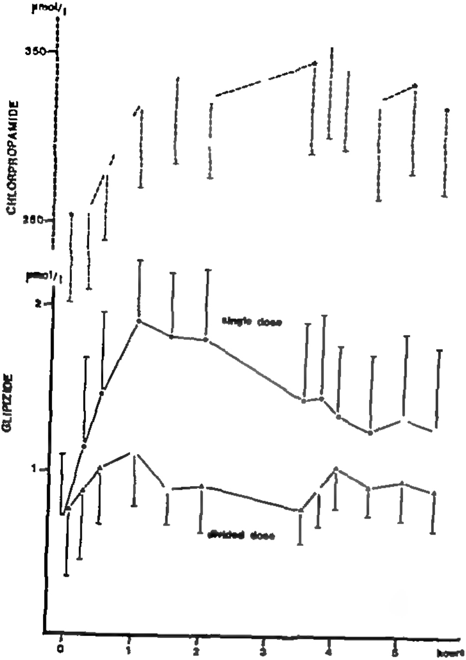

Fig 1 Plasma concentration profiles of chlorpropamide and glipizide (mean and S E.M) during the three different medications, i.e chlorpropamide once daily (intake before breakfast), glipizide once daily (intake before breakfast) and *glipizide in divided dosage (intake before breakfast, lunch and dinner).*

them were obese (>20%) All nine were examined at three different occasions, following three different medications of at least one month s duration The three examinations were identical and were carried out as follows

Examination pr tocol

In order to ascertain identical examination conditions, the following procedure was used One month before the patient was included in the study the individual dietary need was estimated and defined by a dietitian. The patient was carefully instructed to adhere to this dietary regimen. For each examination the patient was admitted to and stayed at the Diabetes Care Unit, Malmö General Hospital during four days with preceding medication maintained During each of the four days the patient was given the individually estimated amount of calories from a weekly menu The menu was different for each of the four consecutive days, but during the three examination periods, the daily series of breakfast lunch and dinner meals was strictly repeated for each patient Thus the individual food intake was identical at the three observation periods.

On the fourth day enous blood was sampled for determination of blood glucose plasma insulin plasma C peptide and plasma chlorpropamide or glipizide Samples were drawn before intake of drug and breakfast and then at 15 30 45 60, 90 120 and 180 min after start of breakfast, and at 15 (=210+15 min after breakfast start) 30 45 60 90 and 120 min after lunch.

Diabines(e) Pfizer Groton Conn. USA.
Min(i)diab® Carlo Erba, Milano Italy

Medication

For at least 6 months, all patients had initially been kept on once daily chlorpropamide[1] 125 mg (n=1) 250 mg (n=4) or 375 mg (n=4). After the first examination had been completed, all patients were switched over to glipizide[2] once daily for one month, 5 mg (n=1), 10 mg (n=1) or 15 mg (n=7). Finally the patients were switched over to glipizide in divided dosage for one month, eight patients were given 5 mg t.i.d., while the ninth patient was kept on 2.5 mg b.i.d. (morning and evening). The latter had been on 125 mg chlorpropamide initially and a single dose of 5 mg glipizide subsequently.

Apart from sulfonylurea, patients 5 and 6 were taking phenformin (50 mg b.i.d.) and patient 3 metformin (500 mg b.i.d.). The biguanide medication was unaltered during the whole course of the study.

Chemical analyses

Blood glucose determinations were carried out immediately after sampling, by the glucose oxidase method (8). For the other analyses, plasma was stored at −20°C until assayed. The concentrations of immunoreactive insulin and C-peptide were determined by radioimmunoassays (9, 10); for the latter antiserum M 1230 was used. The order of sample analyses was arranged so that between-group differences in C-peptide and insulin degradation during storage should be avoided. The plasma concentrations of chlorpropamide and glipizide were measured by gas-liquid chromatography (11) and high-pressure liquid chromatography (12), respectively.

Calculations

Areas under concentration curves were calculated by the trapezoidal rule. Statistical significance was assessed by Student's t-test. Mean values are given with S.E.M.

RESULTS

Fig. 1 demonstrates the mean plasma concentrations of chlorpropamide and glipizide during the three examination days, and Table 1 shows the individual concentrations before tablet and breakfast intake on these days. It can be seen that the chlorpropamide levels were more than 100 times greater than those of glipizide. In addition, it appears that the patients were continuously exposed to chlorpropamide, as large amounts of this drug were present already before intake of the morning dose (Table I).

The glipizide concentrations showed much greater fluctuations than those of chlorpropamide. Indeed glipizide once daily apparently yielded a discontinuous exposure in at least four patients, as judged from the absence of detectable glipizide in their blood before intake of drug and breakfast (Table I). When glipizide had been given in divided dosage, on the other hand, only one patient seemed to have been exposed to sulfonylurea discontinuously (Table I).

Table 1 *Individual plasma concentrations of chlorpropamide and glipizide before intake of drug and breakfast*

0 signifies concentrations below limit of detection, i.e. <22 nmol/l

Patient no.	Chlorpropamide (µmol/l)	Glipizide once daily (nmol/l)	Glipizide in divided dosage (nmol/l)
1	340	0	561
2	264	1 908[b]	1 482[b]
3	466	247	47
4	419	0	225
5		0	56
6	134		
7	174	3 064[b]	3 379[b]
8	145	[illegible]	0
9	90	0	[illegible]

Not available.
Tablets probably taken before blood sample.

The after-breakfast concentrations of glipizide were significantly greater when the whole daily dose was given in the morning than when divided dosage was used. Even after lunch, moreover, the glipizide concentrations remained numerically, albeit not significantly, higher during once-daily administration than after divided dosage, in spite of the 5 mg taken at lunch during the latter regimen (Fig. 1).

The changes in the plasma concentrations of C-peptide following breakfast were similar during the three treatments (Fig. 2), and the areas under the concentration curves did not differ significantly. In contrast, the plasma insulin curves were pronouncedly dissimilar (Fig. 3). Thus, when glipizide was given once daily, the mean ratio of the areas under the plasma insulin concentration curves was about 60% greater than that seen when glipizide was given in divided dosage (paired t-test, $p<0.05$) and about 70% greater than that seen during chlorpropamide treatment (paired t-test, $p<0.05$). The two latter medications, on the other hand, yielded essentially similar plasma insulin curves (Fig. 3).

The after-breakfast increase in blood glucose was significantly smaller ($p<0.05$ in paired t-test on area under the concentration curves) during treatment with glipizide once daily than when divided dosage was used and when chlorpropamide was administered (Fig. 4). The two latter treatments yielded

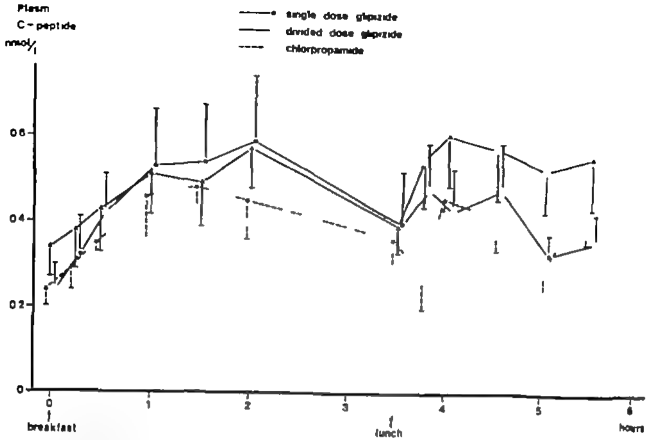

Fig 2 C-peptide concentrations in plasma (mean and S.E.M.) following breakfast and lunch during the three different medications.

similar blood glucose curves after breakfast (Fig. 4)

Following lunch the C peptide increase was significantly greater ($p<0.05$ for area under the curve) during treatment with glipizide in divided dosage than during the other two treatments (Fig. 2) This was associated (Fig. 3) with insignificantly higher plasma insulin levels 1½ and 2 h after lunch and with a significantly greater reduction ($p<0.05$ 2 h after lunch) of blood glucose (Fig. 4)

The mean fasting blood glucose level was lowest during chlorpropamide treatment (9.9±0.7 mmol/l) and highest during treatment with glipizide once daily (11.2±0.6 mmol/l $p<0.05$ paired *t* test) Glipizide in divided dosage yielded an intermediate mean value (10.4±0.8 mmol/l) which did not differ significantly from any of the other two values

DISCUSSION

Chlorpropamide is eliminated very slowly (13) Hence conventional once-daily administration of this drug leads to continuous—i e 24 hours a day—sulfonylurea exposure This was verified in the present material the patients had high plasma concentrations of chlorpropamide already before the morning intake of the drug. As the chlorpropamide concentrations were at least 100 times higher than those of glipizide even though the former drug was not more effective than the latter (*vide infra*) the findings add support to the notion that the intrinsic activity of glipizide is much greater than that of chlorpropamide (cf 14)

In contrast to chlorpropamide glipizide has a short half life (15) implying that glipizide would yield a discontinuous exposure of sulfonylurea if given once daily This was found to be partially correct when on once-daily glipizide at least 4 patients had pre-dose levels of glipizide that were close to zero When on divided glipizide dosage on the other hand at least 5 of the patients seemed to have been exposed continuously As might be expected continuous sulfonylurea exposure was associated with a lower fasting blood glucose level than was discontinuous exposure

The glipizide concentrations after breakfast were considerably higher when the whole daily dose was

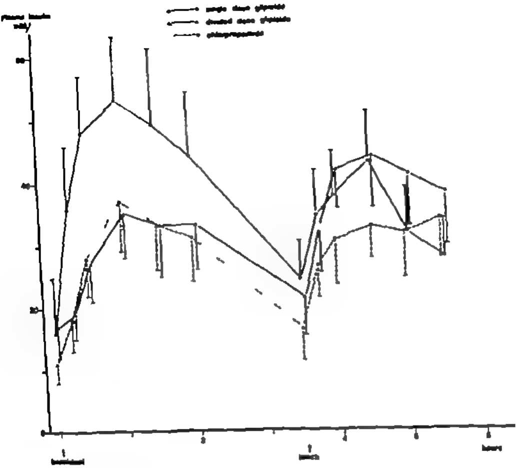

Fig. 3. Immunoreactive insulin concentrations in plasma (mean and S.E.M.) following breakfast and lunch during the three different medications.

given in the morning than when divided dosage was used. Even after lunch, however, the glipizide levels were higher rather than lower during the former than during the latter regimen, despite the second 5 mg dose taken at lunch by 8 of the 9 patients when on divided dosage.

Even though the drug concentrations were highly different, the changes in plasma C-peptide following breakfast were similar during the three treatments. Reasonably this signifies that equivalent amounts of insulin were released from the pancreas into portal circulation. In spite of this, much more insulin apparently reached systemic circulation following breakfast when the whole daily dose of glipizide was administered in the morning than when glipizide was given in divided dosage, or when insulin after breakfast was less pronounced during the former than during the two latter treatments, thus allowing more insulin to reach systemic circulation.

The increase in peripheral insulin also seemed to promote a more effective utilization of glucose, as the blood glucose increase following breakfast was significantly smaller during once-daily glipizide than during the two other treatments.

The possibility of extrapancreatic actions of sulfonylureas has been emphasized previously (2), and animal experiments have evidenced that sulfonylurea can reduce hepatic degradation of insulin (16). Thus, it seems probable that, although no additional enhancement of insulin secretion occurred, administration of the whole glipizide dose in the morning improved the therapeutic effect by re-

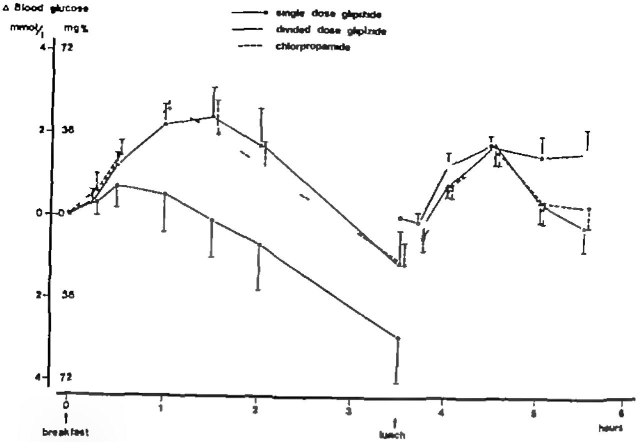

Fig 4 Changes (mean and S E.M) in blood glucose (relative to fasting level) following breakfast and lunch during the three different medications.

ducing hepatic extraction of insulin to a greater degree than did divided glipizide dosage and than did chlorpropamide

It is possible that part of the insulin release actually was proinsulin passing through the liver without extraction However the improved glucose profile during glipizide once daily implies that the increase in immunoreactive insulin indeed represented genuine insulin The improvement would seem to be a direct consequence of the very high glipizide concentrations evoked by the large morning dose but it could also be related to the fact that once-daily glipizide yielded a more discontinuous sulfonylurea exposure than did divided dosage or chlorpropamide If sulfonylureas affect the incorporation of zinc atoms in the formation of insulin hexamers in the B-cells this might result in increased hepatic extraction of insulin during continuous SU exposure while discontinuous exposure would lead to a reduced extraction since zinc amplifies hepatic binding of insulin (17–20)

As sulfonylureas may influence the number of insulin receptors and hence change tissue binding of insulin (4 5) another possibility is that the altered extrapancreatic disposition of insulin resulted from displacement of insulin in various tissues.

The fact that the C peptide responses following breakfast were similar during the three treatments does not support the notion that continuous sulfonylurea exposure—at the concentrations prevailing at night—would impair the biosynthesis of insulin as inferred by in vitro studies on islets (6 7) On the other hand such impairment could be involved in the different C-peptide responses at lunch (*vide infra*)

When on divided glipizide dosage 8 of the 9 patients were given a second 5 mg dose of the drug at lunch This promoted a greater C-peptide response to the lunch meal than that seen during treatment with once daily glipizide or with chlorpropamide In addition there was a greater albeit insignificant increase of plasma insulin and a significantly lower blood glucose level This would seem a logical consequence of the additional glipizide dose It must be

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A possible explanation is that the enhanced effect resulted from the increased glipizide exposure within the gastroenterohepatic region e.g. via mobilization of duodenal insulin-releasing acti ity (DIRA) as shown to occur following glibenclamide administration (2). In addition, the blood glucose reduction could have been amplified by a diminished hepatic output of glucose in turn evoked by the increased glipizide concentration in the portal vein. A recent study has shown that oral sulfonylurea (tolbutamide) administration can provoke a blood glucose reduction at a time when the systemic concentration of the drug still is close to zero (22).

An alternative possibility is that the very high after-breakfast concentrations of glipizide following once-daily administration may have inhibited the biosynthesis of insulin (*vide supra*) leading to reduced mobilization of the hormone following lunch.

In conclusion, the findings favour the opinion that a high sulfonylurea (glipizide) concentration, in addition to promoting pancreatic insulin release may alter the extrapancreatic disposition of the released insulin so that its effect is enhanced. Probably this is due to reduced hepatic extraction of the drug, but it could also result from displacement of tissue-bound insulin. The findings further support the notion that the effect of orally administered sulfonylurea is determined not only by its concentration in systemic blood but also by its gastroenterohepatic appearance The possibility that sulfonylureas may inhibit insulin biosynthesis could neither be confirmed nor refuted Due to its higher potency and shorter half-life glipizide seems to offer greater therapeutic flexibility than chlorpropamide However further studies are required to define the optimum choice and use of sulfonylureas.

ACKNOWLEDGEMENTS

The investigation was supported by grant no 3880 from the Swedish Medical Research Council by grant from the Swedish Board of Health and Welfare (the Dalby project) and by Novo Industri, Malmö, Sweden.

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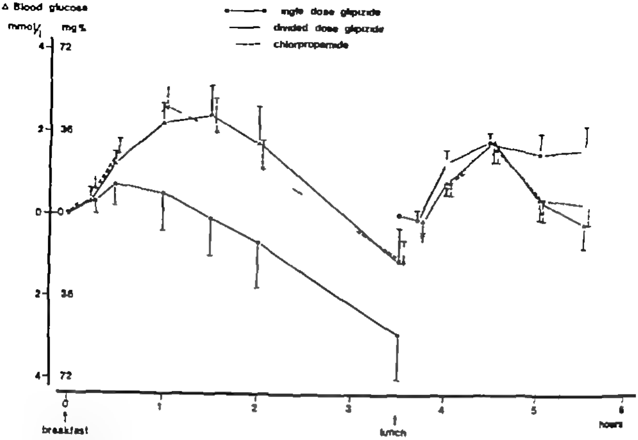

Fig 4 Changes (mean and S E M) in blood glucose (relative to fasting level) following breakfast and lunch during the three different medications.

ducing hepatic extraction of insulin to a greater degree than did divided glipizide dosage, and than did chlorpropamide.

It is possible that part of the insulin release actually was proinsulin, passing through the liver without extraction However the improved glucose profile during glipizide once daily implies that the increase in immunoreactive insulin indeed represented genuine insulin The improvement would seem to be a direct consequence of the very high glipizide concentrations evoked by the large morning dose but it could also be related to the fact that once-daily glipizide yielded a more discontinuous sulfonylurea exposure than did divided dosage or chlorpropamide If sulfonylureas affect the incorporation of zinc atoms in the formation of insulin hexamers in the B-cells this might result in increased hepatic extraction of insulin during continuous SU exposure while discontinuous exposure would lead to a reduced extraction since zinc amplifies hepatic binding of insulin (17–20)

As sulfonylureas may influence the number of insulin receptors and hence change tissue binding of insulin (4 5) another possibility is that the altered extrapancreatic disposition of insulin resulted from displacement of insulin in various tissues.

The fact that the C-peptide responses following breakfast were similar during the three treatments does not support the notion that continuous sulfonylurea exposure—at the concentrations prevailing at night—would impair the biosynthesis of insulin as inferred by in vitro studies on islets (6 7) On the other hand such impairment could be involved in the different C peptide responses at lunch (*vide infra*)

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An alternative possibility is that the very high after-breakfast concentrations of glipizide following once-daily administration may have inhibited the biosynthesis of insulin (*vide supra*), leading to reduced mobilization of the hormone following lunch.

In conclusion the findings favour the opinion that a high sulfonylurea (glipizide) concentration, in addition to promoting pancreatic insulin release may alter the extrapancreatic disposition of the released insulin so that its effect is enhanced. Probably this is due to reduced hepatic extraction of the drug but it could also result from displacement of tissue-bound insulin. The findings further support the notion that the effect of orally administered sulfonylurea is determined not only by its concentration in systemic blood but also by its gastroenterohepatic appearance. The possibility that sulfonylureas may inhibit insulin biosynthesis could neither be confirmed nor refuted Due to its higher potency and shorter half-lif glipizide seems to offer greater therapeutic flexibility than chlorpropamide However further studies are required to define the optimum choice and use of sulfonylureas.

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Acta Med Scand, Suppl. 656, 19–21 1981

Plasma Insulin and C peptide in Normal and Glucose Intolerant Males the Role of Hepatic Insulin Uptake

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ABSTRACT Plasma immunoreactive insulin and C-peptide were measured in the basal and glucose-stimulated state in middle-aged males. Normals were compared with individuals with mild to moderate glucose intolerance. The results demonstrate the value of C-peptide measurements in the assessment of "true" insulin secretion and suggest that a reduced hepatic insulin extraction is a feature of the glucose intolerant state.

Key words insulin, C-peptide, glucose intolerance hepatic insulin uptake.

The role of a reduction in glucose-induced insulin secretion, as opposed to other pathogenetic factors in the mildly glucose intolerant state as well as in type 2 diabetes (MOD) remains controversial

It is recognized that the insulin secretory process is incompletely documented by peripheral plasma immunoreactive insulin (IRI) assays, because of the high and variable hepatic uptake of insulin. Since C-peptide is cleared by the liver to a very minor extent, measurements of plasma C-peptide immunoreactivity (CPR) afford better insight into the actual insulin secretion Simultaneous IRI and CPR assays may be used for an indirect evaluation of hepatic insulin uptake

The above considerations have been applied in the present study on two groups of glucose intolerant middle-aged males, in comparison with matched normal individuals.

SUBJECTS

Males aged 48–50 were investigated as part of population health screening programmes. On the basis of oral glucose tolerance testing (OGTT), normal individuals were differentiated from those with mildly impaired glucose tolerance (IGT) according to proposed criteria (4) The IGT individuals were tested twice, with consistent results. Males of similar age and relative body weight with mild to moderate type 2 diabetes (MOD) were recruited from patients attending diabetic out-patient department.

METHODS

OGTT 30 g glucose (10 g/100 ml) per m² body surface area was administered. EDTA blood samples were taken for the assay of IRI and CPR by the methods of Heding (1 2). In the present study only basal (fasting, 0 min) and 40 min levels were used.

Two groups of subject were selected: (A) individuals with low OGTT IRI increments ("low insulin responders), and (B) subject with high basal C-peptide levels. In both groups comparisons were made between normal and glucose intolerant individuals, the latter comprising both IGT and MOD subjects.

Data subjected to statistical analysis were basal IRI and CPR values, 0–40 min increments, and ratios IRI/CPR. Student' *t*-test was used for evaluation of differences between normals and IGT + MOD

RESULTS

A Low Insulin Responders

Subjects are shown in Table I and data in Fig. 1 and 2. It is apparent that normals had only slightly higher OGTT insulin response as measured by IRI increments. In contrast the CPR increments were considerably higher in the normal group Ratios IRI/CPR of 0–40 min increments were lower in the normal group indicating that these subjects ha a higher hepatic insulin uptake

B Subject ith H gh Basal C-peptide Levels

The study groups are shown in Table II and results in Fig. 3 and 4 Whereas there was no difference in basal CPR between normals and IGT + MOD subjects, the former had lower basal IRI levels. Glucose induced insulin secretion, as measured by IRI and CPR increments was the same in both groups (data not shown) Ratios IRI/CPR, from basal as well as 0–40 min increment data, were lower in the

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Abbreviations MOD = maturity onset diabetes (type 2 diabetes), IRI = immunoreactive insulin, CPR = C-peptide immunoreactivity OGTT = oral glucose tolerance test, IGT = impaired glucose tolerance.

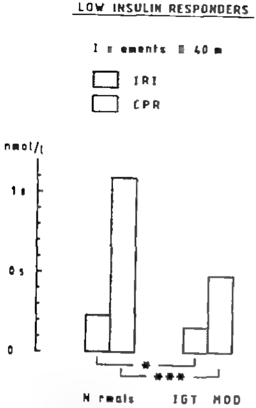

Fig 1 P IRI and P-CPR 0–40 min increments in low insulin responders Significance of differences. $p<0.05$ $p<0.001$

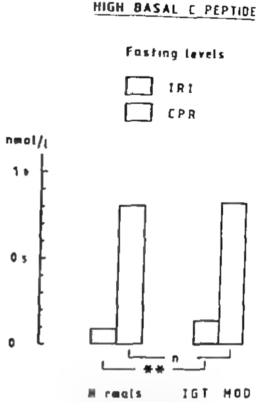

Fig 3 Fasting levels of P IRI and P-CPR in subjects with high basal C-peptide Significance of differences. NS not significant $p<0.01$

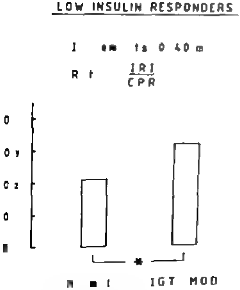

Fig 2 Ratios between 0–40 min increments of P IRI and P-CPR in low insulin responders Significance of difference $p<0.05$

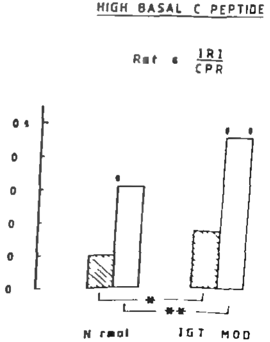

Fig 4 Ratios IRI/CPR fasting and 0–40 min, in subjects with high basal C-peptide Significance of differences. $p<0.05$ $p<0.01$

Table I *Low insulin responders*

OGTT P-IRI increment 0–40 min <0 30 mmol/l. SU = sulfonylurea

	Normals	IGT + MOD
Number	10	11
Age	48–90	37–58
SU treated		4

Table II. *Subjects with high basal C-peptide*

P-CPR fasting >0.70 nmol/l. SU = sulfonylurea

	Normals	IGT + MOD
Number	14	10
Age	48–90	37–58
SU treated		2

normal group Accordingly the extent of hepatic insulin extraction was presumably higher in the normals.

DISCUSSION

With the C-peptide antiserum used (Novo M 1230), cross reaction with proinsulin is minimal being significant only in individuals with large amounts of proinsulin bound to insulin antibodies. Since none of the subjects had received insulin treatment such antibodies were not to be expected. Therefore the CPR values are representative of plasma C peptide concentrations. In contrast IRI measurements are significantly influenced by plasma proinsulin, and the proinsulin proportion of IRI may be higher than has been presumed so far (3) This is a confounding factor since proinsulin has low biological activity but may well undergo slow conversion to insulin in the circulation or in target tissues Also hepatic uptake of proinsulin is low

In conclusion the data indicate that the extent of hepatic insulin uptake may constitute a significant difference between normal individuals and those with minor to moderate degrees of glucose intolerance Since uptake probably largely means receptor contact and biological action insulin influence on the important glucose-regulating processes in the liver may be a major point of difference between the normal and the glucose intolerant state In addition it is obvious that the designation low insulin responder based on peripheral IRI assays has an insecure validity since the actual insulin secretory response is not accurately known.

Further studies will be needed to establish whether an increased proportion of proinsulin in the B cell secretory output is also a common factor in glucose intolerance

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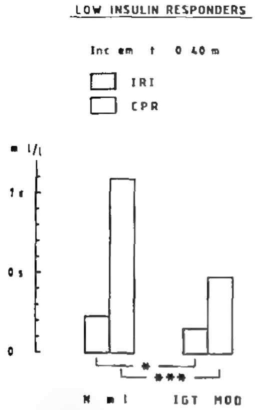

Fig 1 P-IRI and P-CPR 0–40 min increments in low insulin responders" Significance of differences. $p<0.05$ ** $p<0.001$

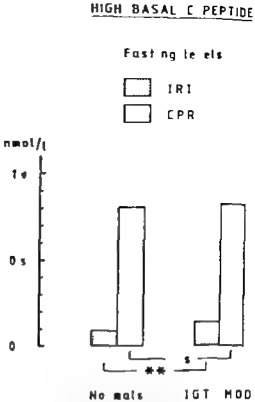

Fig 3 Fasting levels of P-IRI and P-CPR in subjects with high basal C-peptide Significance of differences: NS not significant $p<0.01$

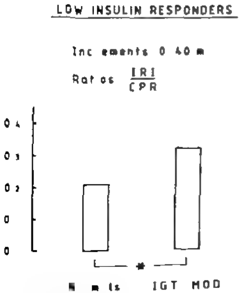

Fig 2 Ratios between 0–40 min increments of P IRI and P-CPR in low insulin responders" Significance of difference. $p<0.05$

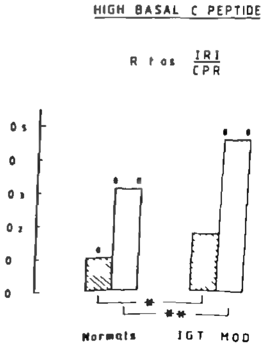

Fig 4 Ratios IRI/CPR fasting and 0–40 min subjects with high basal C-peptide. Significance of differences: $p<0.05$ ** $p<0.01$

Table I *Low insulin responders*

OGTT P IRI increment 0–40 min ≤0.30 nmol/L SU=sulfonylurea

	Normals	IGT + MOD
Number	10	11
Age	48–50	37–58
SU treated		4

Table II *Subjects with high basal C-peptide*

P-CPR fasting ≥0.70 nmol/L SU = sulfonylurea

	Normals	IGT + MOD
Number	14	12
Age	48–50	37–58
SU treated		2

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Acta Med Scand Suppl. 656. 23–27 1981

Reticulocytes and Insulin Binding to Erythrocytes[1]

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ABSTRACT The relationship between erythrocyte insulin receptors and the reticulocytes were studied in group with varying degree of reticulocytosis. The maximal ^{125}I-insulin binding to erythrocytes varied between 6 % and 37 % and it showed a highly significant positive correlation with the reticulocyte count (=0.85). The highest binding was found in a patient with hereditary spherocytosis and very active hematopoiesis (312×10^9 reticulocytes per litre). The results suggest that insulin receptors are predominantly localized to the young erythrocytes, and that further studies are needed to characterize the dependence of the receptor on erythrocyte maturation.

Key ords insulin receptors, erythrocytes, reticulocytes, hereditary spherocytosis.

Determination of insulin receptors in clinical studies has been restricted by the fact that the available methods require either open biopsy (adipocyte receptors) (1 2, 3 4) or collection of excessive amounts of blood (monocyte receptors) (4 5 6, 7). The method for measuring insulin binding to erythrocytes recently described by Gambhir et al. (8) makes it possible to determine insulin receptors more easily even as a routine method in clinical medicine

However Thomopoulos et al. (9) described that in rabbit the binding occurred only to the youngest erythrocytes and that the erythrocytes lost the ability to bind insulin during the process of maturation. In this preliminary investigation we have studied a group of patients with a varying degree of reticulocytosis to evaluate a possible correlation between the proportion of young cells as reflected in the reticulocyte count and the insulin binding to erythrocytes.

MATERIAL AND METHOD

Patients 12 patients were included in this study Some pertinent data are given in Tables I and II.

Erythrocyte preparation. 10 ml blood was collected after an overnight fast in heparinized tubes and analysed ation (10 min, 400×g 20°C) the plasma was aspirated. The erythrocytes (RBC) were separated from other blood cells by a modification of the method of Böyum as reported by Gambhir et al. (8). The red blood cell pellet was resuspended in buffer containing hepes 50 mmol/l, tris 50 mmol/l, $MgCl_2$ 10 mmol/l, ethylenediaminetetra-acetic acid 2 mmol/l, dextrose 10 mmol/l, $CaCl_2$ 10 mmol/l NaCl 50 mmol/l, KCl 5 mmol/l and 0.1% BSA (pH adjusted to 8.0 at 23–25°C). The final cell concentration was 3.5–5 1×10^{12} cells per litre The reticulocytes were counted as described by Atwaker (10).

Iodination of insulin Monocomponent porcine insulin (Novo AS, Copenhagen, Denmark) was iodinated by the lactoperoxidase method according to Thorell and Johansson (11) to specific activity of 190–215 µCi per µg.

Binding studies The incubation of RBC and the separation of insulin bound to RBC from free insulin was performed as described by Gambhir et al. (8) with the following modification. Each assay tube contained 400 µl RBC 25 µl ^{125}I-insulin and varying concentration of unlabelled insulin, in total volume of 525 µl. After incubation, 100 µl of the suspension was aliquoted into prechilled microfuge tubes containing 100 µl of buffer and 100 µl of dibutylphthalate (Merck Schuchardt). The tubes were centrifuged in Beckman microfuge B at 4°C for 2.5 min The tubes were cut above the pellet leaving about 1/5–1/10 of the total dibutylphthalate volume in the bottom of the tube. The radioactivity of the pellet was measured in well type gamma counter (Nuclear Enterprises NE 1600). The correction for unspecific insulin binding was based on the activity in the pellet in tubes containing 5 10^4 ng/ml of unlabelled insulin. The unspecific binding was usually less than 5 per cent.

Binding data were calculated from plots of the specific bound radioactivity versus the bound/free (B/F) ratio according to Scatchard (12).

RESULTS

The maximal specific binding (in tubes containing no unlabelled insulin) varied between 6 1 37 1% The highest binding was found in a patient with hereditary spherocytosis and a high proportion of reticulocytes (312×10^9 per litre = 7.8%) (Fig. 1) Within the whole group there was a highly signifi-

[1] Presented in part at the XXXVI Annual Meeting of the Swedish Medical Association (Acta Societatis Medicorum Suecanae 88 (3) p. 141 1979).

Table I *Clinical and metabolic data*

	Age	Sex	Diagnosis	Therapy	B-Glucose (mmol/l)	P Insulin (mIU/l)	Body-weight (kg)
1	69	F	Hemolytic anemia	Cortisone-Propanolol	4.4	3	65
2	38	M	Healthy[a]	–	5.5	6	84
3	23	M	Hereditary spherocytosis	–	4.0	<3	59
4	71	M	Cardiac failure	Hydrochlorothiazid	4.5	4	68
5	34	M	Liver cirrhosis	–	5.1	68	64
[illegible]	37	M	Healthy[a]	–	4.8	10	80
7	28	F	Healthy[a]	–	4.5	<3	[illegible]
8	10	F	Healthy[a]	–	4.9	<3	30
9	10	F	Healthy[a]	–	5.0	5	29
10	0[b]	F	Hyperviscosity syndrome		4.6	22	[illegible]7
11	0[b]	F	Congenital cardiac abnormalities Mb Down Hyperviscosity syndrome	–	3.4	16	3.8
12	69	F	Sideropenic anemia	–	5.0	6	62
Ref value					3.3–5.6	<20	

[a] Cases studied without abnormality been revealed
[b] Newborn.

cant positive correlation between the binding and the reticulocyte count ($r=0.85$, $p<0.001$) (Fig 2) No correlation was found to other cellular components

The binding capacity calculated from the Scatchard plot was approximately 50 binding sites per erythrocyte (range 10–120) The reticulocyte constituted 0.7–7.8% of the erythrocyte population If the receptor sites instead were assumed to be localized on the reticulocytes only (range 34–312×10⁹ per litre) each of them would contain about 3000 sites per cell (range [illegible]500–5000) In all cases the Scatchard plot was courvilinear The slope of the high avidity component was approximately identical in all cases Fig 3 A and 3 B illustrate the findings in patients with a low and a high reticulocyte count, respectively

DISCUSSION

These results show that the binding of insulin to erythrocytes is related to the number of reticulocytes The clinical conditions and other parameters

Table II *Hematological data*

	Hb (g/l)	Erythrocytes (10^{12}/l)	Leucocytes: Total (10^9/l)	Differential count: Neutrophils (%)	Eosinophils (%)	Basophils (%)	Lymfocytes (%)	Monocytes (%)	Platelets (10^9/l)	Hematocrit (%)	Reticulocytes (10^9/l)
1	116	3.9	5.1	66	0	0	31	3	295	34	156
2	175	4.2	6.5	63	2	0	34	1	160	48	67
3	155	4.0	7.2	68	0	0	30	2	233	40	31
4	183	5.1	5.2	48	5	1	44	2	160	55	82
5	110	3.9	7.0	–	–	–	–	–	[illegible]75	32	141
6	168	4.6	5.4	60	2	0	33	5	253	45	42
7	138	3.9	4.3	46	4	0	47	3	350	42	76
8	138	4.6	5.0	36	0	1	57	6	335	41	34
9	129	4.9	4.2	44	1	0	54	1	185	40	35
10	260	3.4	–	–	–	–	–	–	250	81	184
11	238	3.3	18.4	70	[illegible]	0	27	3	55	80	61
12	50	4.1	8.[illegible]	73	0	1	[illegible]	5	233	–	182
Ref value	115–166	3.7–5.4	4–10	50–70	1–4	0–1	20–50	5–8	125–340	37–49	5–70

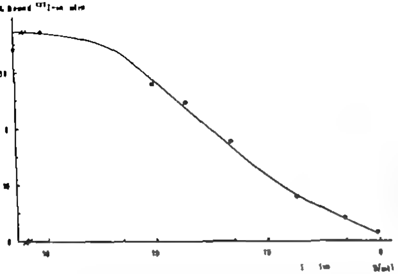

Fig. 1. The per cent of ^{125}I-insulin bound by RBC at various insulin concentrations in patient with hereditary spherocytosis and a high reticulocyte count (312 · 10^9 per litre).

such as age and weight of the patients investigated varied markedly since they were selected primarily because of their reticulocyte count. The rather close relationship found between the insulin binding and the degree of reticulocytosis despite their heterogeneity indicates that the number of reticulocytes is an important denominator for the insulin binding. This relationship has recently been studied by others with divergent results. Eng et al. (13) reported a close correlation but Kappy et al. (14) were unable to find any relationship. The lack of correlation in the study of Kappy et al. may depend on a small variation in the number of reticulocytes which hid the correlation among other factors. This is accentuated by the rather poor precision of available methods for estimating the number of reticulocytes.

HbA$_{1c}$ (%)	S-Vitamin B (pmol/l)	S-Iron (μmol/l)	S-TIBC (μmol/l)
7.0	270	16	[illegible]
[illegible]	380	27	97
6.4	200	[illegible]	73
6.6	260	17	75
7.1	353	22	67
7.3	230	17	66
8.3	450	12	81
7.2	313	[illegible]	79
	230	4	[illegible]
5.8–8.2	110–650	10–35	43–72

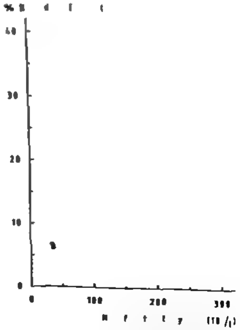

Fig. 2. ^{125}I-insulin binding (%) to erythrocyte receptors as function of reticulocyte count in blood. Corr. coeff. 0.85 ($p<0.001$).

Acta Med Scand Suppl 656: 29–31 1981

On Some Factors Related to the Pathogenesis of Diabetic Angiopathy

L.-O. Almér

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ABSTRACT The deterioration of the circulation in small and large vessels in diabetes seems to be related to abnormalities of the function of the endothelial cells and of the platelets. The endothelial factor VIII R.Ag, enhancing platelet adhesion, is increased while fibrinolysis is decreased. The balance between thromboxane (platelet-aggregating) and prostacyclin (deaggregating) is also shifted in a similar way. These changes all favour increased deposition and delayed removal of platelets and fibrin on the intima, and they might contribute markedly to the development of diabetic angiopathy. Some new drugs seem to normalize the endothelial fibrinolytic activity and long term studies are in progress to evaluate if this improvement is paralleled by a delayed or absent development of vascular complications.

Key words: diabetic angiopathy, platelets, endothelial cells, fibrinolysis.

The purpose of this presentation is not to make a review of all theories about the pathogenesis of vascular complications in longterm diabetes mellitus, but rather to select a couple of pieces of the puzzle that seem to fit together and to be relevant in the deterioration of the circulation.

Although under debate for several decades there is now accumulating evidence that good diabetes regulation will delay the development of diabetic angiopathy. In some individuals the remaining insulin producing reserve of the B cells is sufficient to regulate the blood glucose level within acceptable limits even when the balance between diet, exercise and medical treatment is not perfect. In most long term diabetics, however, strict diabetes control requires more cooperation from the patient than is usually available in the long run. Home blood glucose monitoring is a major step forward, but in the future it is necessary to divert even more time and interest of the medical staff to patient education, so that proper adjustments of therapy can be made quickly by the patients themselves when needed. Hopefully many more patients will benefit from this regimen in the coming years, although it seems that it is not suitable for all diabetics.

However, as long as we are not able to achieve normalization of glucose metabolism in *all* diabetics (through for instance artificial pancreas or transplantation) we will not be able to prevent diabetics from developing macro- and microangiopathy.

Thus there are still very good reasons for studies of the different mechanisms that play a part of the pathogenesis of diabetic angiopathy.

Most of the research was concentrated for a few decades on abnormalities of the capillary basement membrane, but more recent studies have demonstrated that other factors play a more important role.

Fluorescence angiography has shown that there are small areas of non perfusion of the retina quite early, probably caused by occlusion of arterioles, capillaries or venoles. Hypothetically these ischemic areas might explain the later development of microaneurysms and neovascularisation.

What are the causes of these occlusions of the microcirculation? Our group has studied some of the changes of the balance between coagulation and fibrinolysis in diabetes, and we believe the deterioration of the circulation might be explained by abnormal rate of synthesis and release of factors from the endothelium.

In 1974 we reported (8) elevated concentrations of the von Willebrand factor in diabetics, and also that those with microangiopathy had significantly higher levels than the others. This factor, now called F VIII R.Ag, is synthesized in the endothelial cells and is important for platelet adhesion in the subendothelium. Several groups have later confirmed our results. Colwell et al. (5) showed that the normal peak of the diurnal variation of the von

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Willebrand factor activity closely follows the normal peak of growth hormone during the night and after administration of growth hormone to patients with deficiency of this hormone they got a marked increase within 30 minutes of the von Willebrand factor Elevated concentrations of growth hormone is frequently found in diabetics and may induce release of F VIII R Ag from the endothelial cells and this factor will increase platelet adhesion and possibly the tendency to occlusions of the microcirculation This interesting link between endocrinology and coagulation might explain the ameliorating effect of hypophysectomy in some cases of diabetic retinopathy

Many studies have shown that platelets from diabetics when stimulated may aggregate more easily than those of non-diabetics due to an abnormal balance between prostaglandin from platelets (thromboxane) which is said to be increased and from the endothelial cells (prostacyclin) which is reported to be decreased in diabetes

The increased tendency to platelet adhesion and aggregation with concomitant fibrin deposition could be expected to be counterbalanced by an increased activity of the fibrinolytic system

On the contrary we found (2) several abnormalities in the fibrinolytic system in a study of 221 randomly selected diabetics with a range of diabetes duration from a few weeks to 39 years (mean 10 years)

The normal fibrinolytic system seems to be less complicated than the coagulation cascades. The inactive precursor to plasmin is plasminogen a plasma glucoprotein with a molecular weight of 90 000 daltons The activation is caused by an activator synthesized in the endotheial cells and released to the blood stream Its molecular weight is probably about 60 000 daltons and the half-life short less than 30 min

The initial activation step involves activator induced cleavage so that a light and a heavy chain still fixed to each other with disulphide bonds are formed The active site is situated in the light chain and in the heavy chain there are several fibrin binding sites Probably both the activator and plasminogen get attached to the fibrin net before the activation and the plasmin formed will immediately start to degrade the fibrin surface We studied the spontaneous fibrinolotic activity as well as the fibrinolytic response to venous occlusion for 20 min which is the most physiological way to mimic vascular occlusion and to start the activator release mechanism. We were also able to study the vascular fibrinolytic activity using a modification by Pandolfi of the histochemical method of Todd

A biopsy specimen of a superficial dorsal vein of the hand was assessed and in 23% of the 221 diabetics the fibrinolytic activity was abnormally low compared to in 3% in 60 non-diabetic controls. There was a close correlation between the fibrinolytic activity of the temporal artery and the hand vein The response to vascular occlusion was significantly lower ($p<0.001$) in the diabetics than in non-diabetic matched controls and there were six times more "poor responders" in the diabetics. An abnormally low plasminogen activator activity of the vessel walls and/or abnormally low fibrinolytic response to stimulation was seen in 43.4% of the diabetics. The mean fibrinogen level (3.8 g/l) was significantly higher ($p<0.001$) in diabetics and the same was true of the inhibitors of plasminogen activation ($p<0.01$) and of alpha$_2$-macroglobulin ($p<0.001$) which is a plasmin inhibitor

Thus many of the diabetics had a low fibrinolytic activity (plasminogen activator activity) of the vascular walls and a defective activator release to the blood on stimulation and elevated levels of inhibitors of fibrinolysis were also observed

Interestingly those patients who remained free from retinopathy despite long-standing diabetes (more than 10 years) had an almost normal and significantly higher fibrinolytic response to venous occlusion than those who had had diabetes equally long and had developed retinopathy (4)

In diabetes the balance between coagulation and fibrinolysis seems to be shifted to cause a marked tendency to vascular thrombotic occlusions and impaired thrombolysis These abnormlities could be either primary or secondary to the vascular lesions Since the changes were found also early in diabetes and in patients without clinical signs of angiopathy this speaks in favour of a primary defective balance One of the major factors seems to be an abnormality in the endothelial cells concerning synthesis and release of plasminogen activator and F VIII R Ag Very little is known about the regular mechanisms of the synthesis of these substances

The endothelial cells seem to be completely permeable to glucose although membrane receptors for insulin have been reported Abnormally high—or low—glucose levels might thus interfere

with the synthesis and release of endothelial factors. Catecholamines are known to increase the plasminogen activator release via β_2-receptors (7). Since catecholamines are increased in diabetics with marked hypo- or hyperglycemia, this stimulation may be repeated so frequently that the plasminogen activator release eventually will be exhausted and, hypothetically, contribute to the high percentage of "poor responders". Vasopressin might have a similar action.

It is also possible that the autonomic nervous system may play a part, directly or indirectly, on the endothelial function. In another study we found higher plasma levels of F VIII R:Ag and of plasminogen activator activity in diabetics with a tendency to long-standing vasospasm after cooling of the feet, than in those without (1). Autonomic dysfunction is common in diabetes, as reported by our group as well as many others.

Several years ago, Fearnley et al. (6) found that certain drugs, such as sulfonylurea and biguanides could increase the fibrinolytic activity of the blood.

We studied 30 diabetics who had been on chlorpropamide for five years or more. Surprisingly, we found 12 (40%) to have an abnormally low plasminogen activator activity of the vessel biopsies; this prevalence was much higher than in the previously mentioned material of 221 diabetics with various types of therapy (23%). Chlorpropamide was then discontinued and two well-matched patient groups were formed. Fifteen of the patients were put on glipizide and 15 on gliclazide, on doses that gave approximately the same blood glucose control as before. After six to nine months all patients had a normalized fibrinolytic activity of the vessels walls, and still after two years they all remained normal. Thus it is possible that therapy with gliclazide and glipizide may result in a normalization of the vascular fibrinolytic activity permanently.

Presently, long term studies with fluorescence angiography etc. are done to test the hypothesis that these drugs may have a beneficial effect, delaying or even preventing the development of retinopathy.

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Acta Med Scand, Suppl. 656. 33–36 1981

Chlorpropamide alcohol Flushing in Relation to Macroangiopathy and Peripheral Neuropathy in Non insulin Dependent Diabetes

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ABSTRACT Seventy patients with non-insulin dependent diabetes (NIDD) were studied for the chlorpropamide-alcohol flush (CPAF), first degree family history of diabetes, macroangiopathy and for peripheral neuropathy Positive CPAF challenge tests were found in 65% of the tested subjects and in 77% if there was a family history of diabetes. Signs of macroangiopathy (loss of foot pulses) were significantly ($p<0.05$) less common in the CPAF positive than in the CPAF negative diabetics with a duration of diabetes of ten years or less. With a longer duration this difference between the two groups was reduced. Also signs of peripheral neuropathy (abnormal vibration sense) were less common ($p<0.05$) in the CPAF positive diabetics than in the CPAF negative. Previously a low prevalence of retinopathy in the CPAF positive non-insulin dependent diabetics has been reported. We have shown that this is also true of peripheral macroangiopahy and peripheral neuropathy Chlorpropamide-alcohol flushing seems to be related to relative protection against late complications in diabetes and the test might be used to find patients at risk.

Key words chlorpropamide-alcohol flushing, macroangiopathy peripheral neuropathy non-insulin dependent diabetes mellitus

A well-known side effect of chlorpropamide medication in some diabetics is facial flush after drinking alcohol. This was first reported more than 20 years ago (1). In 1978 Leslie and Pyke showed this chlorpropamide alcohol flush (CPAF) to be an autosomal dominant inherited trait associated with non-insulin dependent diabetes mellitus (NIDD) (3 5) In their studies 50–60% of the diabetics with NIDD were flushers and of those with a first degree family history of NIDD 80% were flushers. Retinopathy was uncommon in the flushers and if present, much milder than in non flushing diabetics with NIDD (2) The flush was thought to be mediated by endogenous opiates and by prostaglandins as the flush could be reduced by naloxone and aspirin, respectively (4 6).

As the flushing diabetics seemed to have a diabetes with less retinopathy (microangiopathy) we wanted to study the relations also between CPAF and angiopathy of the large vessels (macroangiopathy) and peripheral neuropathy in NIDD

SUBJECTS AND METHODS

Seventy patients with NIDD, 28 females and 42 males were tested for CPAF The mean age was 70 (range 58–83) years and the mean duration of diabetes after diagnosis was 10 (4–22) years. 13 patients were on diet only 22 patients were on maintenance therapy with chlorpropamide (4 patients were on 125 mg, 12 were on 250 mg and 6 were on 375 mg daily) and 35 patients were on other sulphonylurea drugs.

Twelve hours before the test the patients were given 250 mg of chlorpropamide (Diabinese, Pfizer) orally although the patients treated with chlorpropamide had their prescribed dosages in the morning. The test was performed around 10 a m in a room with constant temperature The skin temperature was measured 2 cm below the lateral canthus of the left eye every 5 min for 20 min before the patients received 8 g of alcohol in fruit juice. A sensitive temperature probe from Electrolaboratory Copenhagen was used After the alcohol administration the skin temperature was measured another 30 min. If a notable flush was seen the patient felt facial warmth and the rise in skin temperature was more than 1°C the test was regarded as positive If the criteria were not fulfilled the test was regarded as negative.

Presence of first degree family history of diabetes and of therapy demanding hypertension were recorded The foot pulses (a. dorsalis pedis and a. tibialis posterior) the patella tendon and the Achilles tendon reflexes were examined. The vibration sense was measured on the medial malleols by Bio-thesiometer These clinical registrations were done without the examiner knowing the results of the CPAF challenge tests.

Statistics

All results were analyzed with linear logistic regression analysis.

Table I *Chlorpropamide-alcohol flushing (CPAF) first degree family history of diabetes and hypertension in 69 non insulin dependent diabetics*

NIDD's	No	CPAF (%)	Family history (%)	Hyper ten-sion (%)
CPAF-positive	45		44	33
CPAF-negative	24		25	17
Family history	26	77		23
No family history	43	58		30
Hypertension	19	79	32	
Total	69	65	38	28

Table III *Chlorpropamide-alcohol flushing (CPAF) and macroangiopathy in 44 patients with non-insulin dependent diabetes for 10 years or less*

		Palpable foot pulses			
NIDD's	No	3–4 (%)	1–2 (%)	0 (%)	
CPAF-positive	28	[illegible]	7	4	p<[illegible]
CPAF-negative	[illegible]	56	25	19	
Family history	13	92	8	0	
No family history	*31*	*71*	*16*	*13*	
Total	44	77	14	9	

RESULTS

Forty five of the tested 70 patients with NIDD fulfilled the three criteria for flush and therefore were regarded as CPAF positive In one female patient the rise in skin temperature was 1 2°C but there was no notable flush seen and the patient did not feel facial warmth This patient was therefore not included in the rest of the study 24 patients did not fulfill the criteria and consequently were regarded as CPAF-negative (see Table I) In the CPAF-positive the mean basal skin temperature was 32.2°C (range 31 0–33.5°C) and in the CPAF-negative 32 8°C (range 31 2–34 6°C) (N S)

In the CPAF-positive the mean increase [illegible] skin temperature was 3 2°C (range 1 0–5 1°C) and in the CPAF-negative 0 3°C (range 0–0 8°C) (p<0 001) During the flush no other symptoms were seen except for redness of the eyes in one patient. The prevalence of first degree family history of diabetes in relation to the presence of CPAF is presented in Table I The prevalence of diabetics treated for hypertension in relation to CPAF is also seen in Table I There were no significant differences in diabetes regulation obesity or smoking habits between the groups.

Age duration and sex

The mean ages were 70 years in both groups and the mean duration of diabetes after diagnosis was 10 years in the CPAF-positive and 9 years in the CPAF-negative group Twenty-two of the CPAF positive but only 5 of the CPAF-negative patients were females (p<0 02)

Peripheral circulation

In Table II the prevalence of palpable foot pulses in relation to the presence of CPAF first degree family history of diabetes and hypertension are presented

Table III shows that in those with short duration, ten years or less, 89% of the CPAF-positive but only 56% of the CPAF-negative patients had (3 or) 4 palpable foot pulses and conversely no palpable foot pulses were found in 19% of the CPAF-negative but only in 4% of the CPAF-positive patients (p<0 05) These findings were striking, because the mean diabetes duration (7 years) was the same in both subgroups and the mean age similar (69 and 70 years, respectively)

Neurological examination

Tendon reflexes In Table IV remaining patellar tendon and Achilles tendon reflexes in relation to the presence of CPAF and a family history of diabetes are presented. If the patellar tendon reflexes were lost the Achilles tendon reflexes always were lost as well In 25% of the CPAF negative but only

Table II *Chlorpropamide-alcohol flushing (CPAF) and macroangiopathy in 69 non-insulin dependent diabetics*

		Palbable foot pulses		
NIDD's	No	3–4 (%)	1– (%)	0 (%)
CPAF-positive	45	76	11	13
CPAF-negative	[illegible]	54	29	17
First degree family history	26	77	15	8
No family history	43	63	19	[illegible]
Hypertension	19	79	5	16
Total	69	68	17	15

Table IV *Chlorpropamide-alcohol flushing (CPAF) and peripheral neuropathy in 69 non-insulin dependent diabetics*

NIDD's	No.	Prevalence of tendon reflexes: Patella & Achilles (%)	Patella (%)	0 (%)	Vibration sense: Normal (%)	Probably abnormal (%)	Abnormal (%)
CPAF-positive	45	56	36	9	36	47	18 $p<0.05$
CPAF-negative	24	42	33	25	17	46	38
First degree family history	26	54	35	12	31	54	15
No family history	43	49	35	16	28	42	30
Total	69	51	35	14	29	46	[illegible]

in 9% of the CPAF-positive patients an areflexia of the lower limb was found (N.S.)

Vibration sense. From previous studies in age-matched non-diabetics a vibration threshold at 20 units or less on the Bio-thesiometer was known to indicate abnormal vibration sense and a vibration threshold at more than 40 units to indicate a clearly abnormal vibration sense. The registration of 21 to 40 units was regarded to indicate probably abnormal vibration sense.

The vibration sense in relation to the presence of CPAF and a family history of diabetes is presented in Table IV. A clearly abnormal vibration sense was found in 38% of the CPAF-negative but only in 18% of the CPAF-positive patients ($p<0.05$).

DISCUSSION

The results indicate that the susceptibility to peripheral vascular disease and peripheral neuropathy in non-insulin dependent diabetics is reduced if the patient is a chlorpropamide-alcohol flusher. More than three-fourths of the studied diabetics with a known family history of diabetes were CPAF-positive, which is comparable to the results of Pyke and Leslie (5). Significantly more women than men were flushers.

In this study absent foot pulses were taken as signs of angiopathy of the large vessels (macroangiopathy). We found that macroangiopathy was four times less common in CPAF-positive than CPAF-negative diabetics with a duration of NIDD for 10 years or less, but after 10 years the CPAF-positive patients seem to be less protected. A puzzling result was the prevalence of hypertension in 33% of the CPAF-positive diabetics but only in 17% of the CPAF-negative. Surprisingly the hypertensive diabetics did not have more signs of macroangiopathy than the normotensive. As expected signs of peripheral neuropathy were common in patients with a long mean duration of diabetes after diagnosis. Signs of peripheral neuropathy were seen more often in CPAF-negative diabetics and advanced peripheral neuropathy was two to three times more common in the CPAF-negative than in the CPAF-positive patients with NIDD.

The prevalence of macroangiopathy and especially peripheral neuropathy were about as low in the group of diabetics with a family history of diabetes as in the CPAF-positive group which was related to the marked overlap between these two groups.

In conclusion, the reported low prevalence of angiopathy of the microvasculature (2) in the CPAF-positive diabetics is evidently also true of the peripheral macrocirculation within the first ten years after diagnosis of non-insulin dependent diabetes. More surprisingly, only a moderate susceptibility to peripheral neuropathy was present in the CPAF-positive diabetics compared to the CPAF-negative. In some way the ability to flush on alcohol after chlorpropamide is related to a relative protection against late complications in diabetes. The CPAF-negative patients with NIDD are more liable to late complications in diabetes and therefore hypothetically should be more strictly controlled although the prophylactic effect of improved metabolic control in this particular group remains to be proven.

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Acta Med Scand Suppl. 656: 37–38, 1981

Chlorpropamide alcohol Flushing and Blood Kinins

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ABSTRACT In pilot study six patients with non-insulin dependent diabetes, three positive and three negative to chlorpropamide-alcohol flushing (CPAF), were tested. The patients were tested both without and with chlorpropamide premedication. Blood kinin concentrations were determined before and after ingestion of small quantities of alcohol. No rise in blood kinin concentrations were found during the flush suggesting that kinins do not play a major part in chlorpropamide-alcohol flushing

Key ords blood kinins, chlorpropamide-alcohol flushing

The tendency to flush after small amounts of alcohol when taking chlorpropamide is inherited as an autosomal dominant trait in non-insulin dependent diabetes mellitus (5), and much effort has been made to understand what is causing this chlorpropamide-alcohol flush (CPAF) The CPAF positive diabetics are reported to have a lower prevalence of diabetic retinopathy (4) as well as macroangiopathy and peripheral neuropathy (3) than CPAF negative diabetics.

This could mean that a negative CPAF test is an early and important marker of those at risk. The biochemical basis for the flush might also in some way be related to some protecting factor delaying the development of lat diabetic complications. This makes the biochemical basis of the flush of great interest.

Leslie et al. (6) reported that endogenous opiate can induce a flush similar to CPAF and that CPAF can be blocked by the specific opiate antagonist naloxone Strakosch et al. (7) later reported that the flush can be blocked by aspirin, which was thought to be an effect of aspirin blocking the prostaglandin (PG) synthesis. Horrobin and Manku (1) suggested that alcohol and activation of one type of opiate receptor enhance PGE biosynthesis by human platelets, and that this is the mechanism of the flush.

When infused intravenously kinins will induce a flush similar to CPAF It is also known that kinins promote biosynthesis of PGE This made it seem worthwhile to study the kinins for any correlation to CPAF

SUBJECTS AND METHODS

Six patients with non-insulin dependent diabetes (NIDD) were studied. From previous tests we knew that three were CPAF positive and the other three were negative. Each patient now passed two tests. The skin temperature was measured 2 cm below the lateral canthus of the left eye every 5 min 20 min before and during the tests with sensitive temperature probe (Electrolab Copenhagen). At the first time the patients were given 8 g ethanol in fruit juice. Samples for determination of blood kinins were taken in chilled syringes containing phenanthroline before precipitation in ethanol immediately before and then 15 and 30 min after the administration of ethanol. The next time, couple of days later the patients had 250 mg chlorpropamide in the evening before the test, and then exactly the same procedure as above was used. The concentrations of blood kinins were determined by radioimmunoassay (2).

RESULTS

No one of the six patients flushed during the test without premedication with chlorpropamide, but during the second test the three CPAF positive patients flushed while the three negative did not. The mean increase in skin temperature after 30 min was 1.2°C during the flush but only 0.5°C if no flush was noted. During the flush there was no rise in blood kinin concentrations and the levels remained virtually unchanged after chlorpropamide and alcohol in CPAF positive as well as negative patients. However without premedication with chlorpropamide alcohol induced slight but not significant decrease in all six patients (Table I).

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Acta Med Scand Suppl. 656: 39–41 1981

Glycosaminoglycan Synthesis by Human Diabetic Normal Adult and Embryonic Fibroblasts in Relation to Insulin Levels

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ABSTRACT Sulfated glycosaminoglycan synthesis by human diabetic, non-diabetic, and embryonic cells was studied. No effect of insulin on net synthesis was noted. Thus, the data do not indicate a role for total sulfated glycosaminoglycan production in the diabetic connective tissue disturbances mediated by insulin.

Key words: sulfated glycosaminoglycans, insulin, fibroblasts

The most evident features of diabetic microangiopathy are an increase in microvascular basement membrane material, as well as deviations from normal in its composition. The fibroblast demands interest as a major source of these connective tissue constituents, mainly collagen and glycosaminoglycans. Furthermore the diabetic fibroblast has attracted interest because of findings of reduced in vitro proliferative capacity (4, 10). Although evidence to the contrary has also been reported (8), the above data and other studies (5, 9) suggest that the diabetic gene or genes may be expressed in the cultured fibroblast.

The possibility of altered synthesis of glycosaminoglycans (GAG) in diabetes was raised by the finding of altered GAG composition in human diabetic kidneys (1). Pronounced reduction of skin GAG was noted in rats when made diabetic with alloxan (7). The administration of insulin almost entirely restored the affected GAG to normal values.

Since both uronic acid and hexosamine derive from glucose, and since insulin regulates the utilization of glucose there is a possible role for insulin as a modulator of GAG biosynthesis.

MATERIALS AND METHODS

Skin punch biopsies were obtained from the inner aspect of the left overarm in four males (age 22, 26, 34 and 26), insulin-dependent, tightly controlled, juvenile-onset diabetics (JOD). Fibroblasts in culture were also established from 3 non-diabetic males, aged 51, 49 and 48. Abdominal skin biopsies from four human embryos (week 15–25) were also cultured. Cells were routinely grown in Medium 199 with Earle salts and 20 mM HEPES buffer (Flow Laboratories) supplemented with 0.1 mg/ml gentamicin, 585 mg/l L-glutamine and 10% fetal bovine serum, heat inactivated. In experimental situations serum was omitted and the medium was sulfate-poor Medium 199. The cells were exposed to radioactive tracer ^{35}S-sulfate, 40 μCi/ml medium, and insulin (Actrapid, NOVO) in various concentrations for 24 hours in 10 cm^2 plastic Petri dishes (Nunc AS) (if not otherwise stated). Sulfated GAGs (S-GAG) were measured in the medium with a cetylpyridinium chloride precipitation procedure (11). Radioactivity was counted in a Packard B2450 scintillation spectrometer and results were expressed as counts per minute (CPM). Net synthesis of S-GAG was calculated as amount of radiotracer incorporated per microgram DNA. DNA was determined by a diaminobenzoic acid fluorometric method (3).

Calculations. The mean CPM/μg DNA for control dishes in each experiment was corrected to 1000 and experimental dishes adjusted accordingly. Dishes from several experiments were pooled, and Student's unpaired *t*-test was utilized.

RESULTS

Embryonic skin fibroblasts did not change S-GAG synthesis when exposed to insulin concentrations 0.1–10 mU/ml (Fig. 1 and Fig. 2). In one set of experiments there was a decrease in synthesis with higher insulin concentration, 100 mU/ml. This could however not be confirmed with the same cells in microwell and multiwell cultures. Neither did diabetic (Fig. 3) or non-diabetic (Fig. 4) fibroblasts show any influence of insulin on S-GAG synthesis.

DISCUSSION

It is probable that the accumulation of S-GAG in connective tissues and basement membranes is influenced in vivo by local regulating factors that may or may not be influenced by insulin or glucose levels. Formation of basal lamina has been pro-

Table I *Blood kinin concentrations in µg/l (mean ± S E.M) before and after ethanol intake in 6 non-insulin dependent diabetics without and with chlorpropamide premedication*

	Time (min)		
	0	15	30
CPAF positive patients (n=3)			
Without chlorpropamide	*0.55±0.07*	*0.32±0 04*	*0.55±0 15*
With chlorpromide	0 40±0 15	[illegible] 43±0 09	0.38±0 06
CPAF negative patients (n=3)			
Without chlorpropamide	0.39±0 03	0.35±0 02	0.22±0 [illegible]
With chlorpropamide	0.45±0 05	0 41±0 02	0 42±0.04

DISCUSSION

Kinins will when infused intravenously induce a flush very similar to the chlorpropamide alcohol flush and they promote biosynthesis of prostaglandin E Since it has been suggested that PGE as well as endogenous opiates are involved in CPAF and that alcohol and opiates enhance PGE biosynthesis by human platelets blood kinins could be an important factor causing CPAF However in this pilot study no increase of blood kinins during the flush was found Thus it seems that kinins most likely do not play a major part in the chlorpropamide-alcohol flush

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Fig 1 No significant difference in S-GAG synthesis (CPM/µg DNA) with insulin levels 0–10 mU/ml but less synthesis in high insulin concentration was noted ($p<0\ 005$) Number of individuals in brackets Number of dishes noted (*n*)

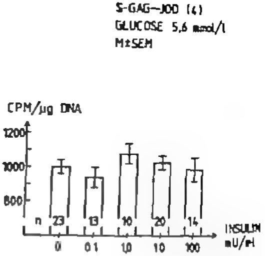

Fig 3 Juvenile onset diabetic cells are not influenced by insulin. Number of individuals in brackets. Number of dishes noted (*n*)

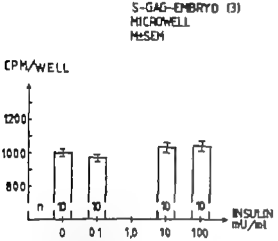

Fig 2 No significant difference n S-GAG synthesis (CPM/well [Linbro Flow])

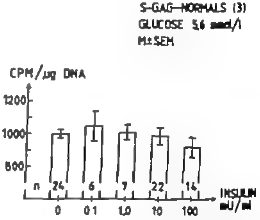

Fig 4 The S-GAG synthesis (CPM/µg DNA) is not influenced by insulin. Number of dishes noted ( ).

posed to result from collagen-mediated reduction in degradation of GAG-containing molecules (2) In this regard it may be pertinent that insulin stimulates the in vitro synthesis of collagen by diabetic skin fibroblasts (6)

It was concluded that insulin exerts no influence on the amounts of extracellular S-GAG produced. Furthermore there was no evident difference between diabetic and non-diabetic cells.

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Acta Med Scand, Suppl. 656: 43–45 1981

A Sensitive Orthostatic Test on Tilt Table Useful in the Detection of Diabetic Autonomic Neuropathy

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During the last decade sensitive autonomic neuropathy (AN) tests have been introduced (1). A reliable method is the deep breathing test (3, 5) in which an impaired variation of the R–R intervals to deep breathing reflects vagal neuropathy. The immediate heart rate reaction to standing up can also be abnormal in AN (2). In that procedure, as in the deep breathing test, a close patient cooperation is needed. Then it is more attractive to use a passive orthostatic tilt table test for AN evaluation. Recently we reported about such a procedure (4). In this presentation some of our experience in asymptomatic diabetics will be reported.

PATIENTS AND METHODS

Forty-six insulin dependent diabetics without symptoms of AN (postural- or gastrointestinal symptoms, gustatory sweating, bladder dysfunction, total impotence or ejaculatory dysfunction) were investigated for AN as well as for peripheral neuropathy (PN). All patients were without evidence of cardiac failure or renal insufficiency and were on no medication apart from insulin. Twenty-six of the patients had diabetes of short duration (5–19 years, mean 11) and the remaining 20 patients had diabetes of long duration (21–49 years, mean 33). Two age-matched control groups were used. Twenty-one healthy young control subjects were matched with the 26 diabetics of short duration and 24 older healthy controls were matched with the 20 diabetics of long duration.

Procedures. Examination of the nervous system included analyses of tendon reflexes and vibration sense. Vibration sense thresholds (Bio-Thesiometer) were determined over the medial malleoli. Threshold values above the mean of the controls +2 S.D. were considered abnormal. Absent ankle reflexes and/or abnormal vibration sense were considered signs of PN. The orthostatic test has recently been presented in detail (4). In brief, fast ( ) head up tilt (90°) was performed on a tilt table during continuous ECG recording. To evaluate the nervous regulation of the immediate heart rate response, atropin (0.5 mg i.v.) as well as propranolol (10 mg i.v.) were given to healthy control subjects. The orthostatic ratios were analysed by two-tailed Mann-Whitney U-test.

RESULTS

Controls. The heart rate reaction to tilting was characterized by a biphasic response (Fig. 1) with an initial acceleration (shorter R–R intervals) followed by a transient deceleration (longer R–R intervals). To describe the heart rate changes, the acceleration index ((resting R–R interval − shortest R–R interval/resting R–R interval)×100) as well as the brake index ((longest R–R interval − shortest R–R interval/resting R–R interval) ×100) were estimated (4).

Atropin injections almost abolished the deceleration phase and the brake index was substantially reduced (Fig. 2). Atropin also gave an impairment in the acceleration phase and the acceleration index was reduced. Propranolol gave a more pronounced impairment of the acceleration with lower acceleration indices than after atropin.

Diabetics. PN was present in 7 diabetics of short duration and in 14 of long duration. In diabetics with PN of short as well as of long duration the immediate heart rate reaction to tilting was characterized by an impairment of the deceleration (Figs. 3–4). The brake index (Fig. 5) was also significantly lower in patients with PN than in those without ($p<0.05$ in short and $p<0.01$ in long duration) as well as in controls ($p<0.01$ in short and $p<0.001$ in long duration). In long duration, an impaired acceleration was shown in diabetics with PN (Fig. 4). The acceleration index (Fig. 6) was significantly lower in these patients than in those without PN ($p<0.05$) as well as in controls ($p<0.001$).

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5 Distribution of the brake index. Horizontal bar = ian. C = controls NPN = diabetics without peripher neuropathy PN = diabetics with peripheral neuro- hy

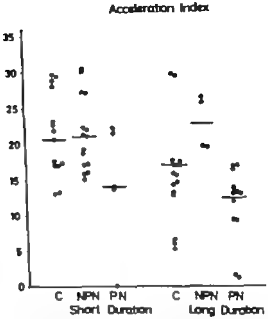

Fig 6 Distribution of the acceleration index. Horizontal bar = median. C = controls. NPN = diabetics without peripheral neuropathy PN = diabetics with peripheral neuropathy

cological test showed that the deceleration phase nly is vagal dependent Vagal mechanism is also portant for the acceleration although an addition- sympathetic mechanism is essential for the accel- tion.

In diabetics close correlation between PN and pairments in the deceleration was shown When e duration of diabetes increased, an impairment in e acceleration also was shown in PN

In conclusion our study shows that AN is fre sent in asymptomatic diabetics with PN The uestion whether AN is an aggravation of PN is nder study in our laboratory

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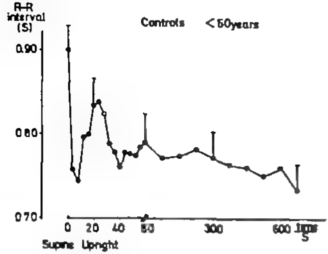

Fig 1 Heart rate changes during the orthostatic test in young control subjects ($n=21$) Vertical bars=1 S E.M

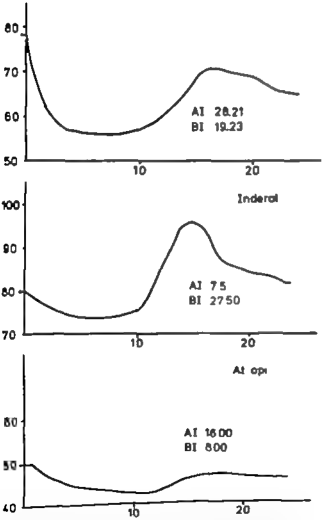

Fig 2 The immediate heart rate reaction in a healthy control subject before (at the top) and after propranolol (in the middle) as well as after atropin (below) intravenously On the abscissa time in seconds and on the ordinate R–R intervals in csec AI=acceleration index. BI=brake index

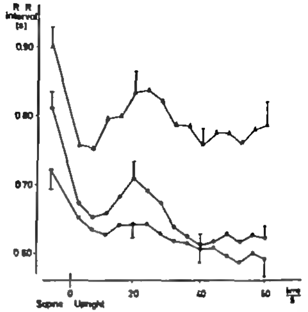

Fig 3 Heart rate before and during the first minute after tilting in diabetics of *short* duration and matched controls. Vertical bars=1 S E.M Δ—Δ, controls ($n=21$); O—O, diabetics without peripheral neuropathy ($n=19$); ●—● diabetics with peripheral neuropathy ($n=7$).

DISCUSSION

The present study shows that the characteristic heart rate reaction to tilting is an initial acceleration followed by a transient deceleration The phar

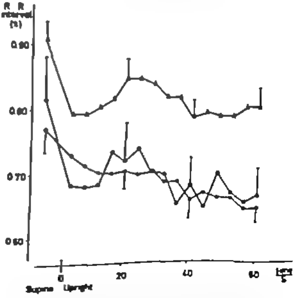

Fig 4 Heart rate before and during the first minute after tilting in diabetics of *long* duration and matched controls. Vertical bars=1 S.E.M Δ—Δ control (=24)· O—O diabetics without peripheral neuropathy (=6)· ●—● diabetics with peripheral neuropathy ($n=14$)

Acta Med Scand Suppl. 656. 47–50 1981

Dietary Fibre in Type II Diabetes

N.-G. Asp, C. D. Agardh, B. Ahrén, I. Dencker, C.-G. Johansson, I. Lundquist, M. Nyman, G. Sartor[a] and B. Scherstén[a]

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ABSTRACT. Recent studies have indicated that diets rich in digestible carbohydrates and dietary fibre might be beneficial in the regulation of type II non insulin dependent diabetes (NIDD). Addition of the gel forming type of dietary fibre such as pectin and guar gum to meals or glucose solutions reduces postprandial glucose and insulin response. Addition of cereal fibres in the form of bran seems to have long term beneficial effect improving glucose tolerance. Little is known, however, concerning effects of dietary fibre naturally occurring in food on postprandial glucose and hormone response. In the present study we prepared two breakfast meals which were similar regarding digestible carbohydrates but differed in their dietary fibre content. One of the meals, including whole grain bread and whole apples, contained 8.4 g of dietary fibre, and the other one, containing white bread and apple juice, 3.1 g. When given to eight NIDD, the fibre rich breakfast gave significantly lower blood glucose increment during the three hours following ingestion. The results indicate that foods rich in dietary fibre might be useful in the regulation of type II diabetes.

Key words: diabetes, carbohydrates, dietary fibre.

The diet used in Sweden as well as in most other western countries to regulate diabetes is hitherto recommended to contain a restricted amount of carbohydrates, an abundant supply of protein and a restricted amount of fat. Recent studies (1, 9), however, have indicated that a high carbohydrate diet rich in dietary fibre might be a better choice for certain patients with type II diabetes (NIDD), reducing fasting and postprandial plasma glucose. It has been suggested that the high carbohydrate and low fat content of these diets is most important and that the high dietary fibre content plays an additive synergistic role in improving glucose tolerance (1).

Complex carbohydrates, i.e. starch, is recommended to diabetics instead of low molecular weight carbohydrates such as monosaccharides or sucrose, since the latter are regarded to be absorbed much more rapidly in the intestine. There is no firm experimental support, however, for the assumption that hydrolysis of starch by amylase is a rate limiting step in its absorption. As early as 1957 Borgström et al. (4) demonstrated that the amylase activity in duodenal juice is high enough to hydrolyse starch in a meal within minutes. Many studies have shown that the monosaccharide absorption is rate limiting for intestinal uptake of carbohydrates. Wahlqvist et al. (18) demonstrated that glucose given as monosaccharide, pentasaccharide or polysaccharide (starch) gave the same blood glucose, insulin and free fatty acid response in healthy volunteers.

Thus, other factors than the molecular size of absorbable carbohydrates must be responsible for the well known clinical experience that starchy foods are preferable as carbohydrate source in the diabetic diet. Such factors might be the content of dietary fibre, which is generally higher in starchy foods than in e.g. sucrose rich foods, the degree of disruption of cells in the food stuffs (6), and possibly amylase inhibitors that occur in many unrefined vegetable foods (12, 19).

Dietary fibre is defined as the sum of polysaccharides and lignin that are resistant to enzymes produced in the human gastro-intestinal tract, and therefore pass the small intestine without being hydrolyzed or absorbed (17). The main polysaccharides included in the dietary fibre concept are cellulose, hemi-cellulose and pectins and other gel forming polysaccharides, such as guar gum, alginates and vegetable gums.

Abbreviations: NIDD = non insulin dependent diabetes, CGM = continuous glucose monitoring.

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Abbreviations: NIDD = non insulin dependent diabetes, CGM = continuous glucose monitoring.

Table I *Composition (g) of breakfast meals with different dietary fibre content*

	A	B
Low fat (0.5%) milk	100	100
Cheese (28% fat)	25	25
Margarine (45% fat)	15	15
Whole grain wheat and rye bread	78	–
White wheat bread	–	75
Whole apple edible parts	100	–
Apple juice	–	100

Table II *Analysis of test meals (g/meal)*

	A	B
Protein	16.0	14.3
Fat	17.5	16.5
Glucose	1.6	1.6
Fructose	5.6	5.8
Galactose	<0.1	<0.1
Sucrose	2.1	2.1
Lactose	5.0	5.3
Starch	30.7	30.8
Dietary fibre	8.4	3.1
Energy*		
KJ	1 660	1 600
Kcal	398	383

* Assuming no energy value of the dietary fibre

Addition of pectin and/or guar gum to meals or glucose solutions has been repeatedly shown to reduce postprandial plasma glucose and insulin in both healthy volunteers and diabetics Several authors have suggested that the improvement in glucose tolerance by these viscous fibres is due to slower absorption of the carbohydrate From some studies it has been concluded that this might be due both to a slower gastric emptying rate and to a slower small intestinal absorption (for review see 7) Others however (8) have found evidence of an increased gastric emptying rate after addition of guar gum or bran

The possibility that dietary fibre influences glucose tolerance by more or less direct effects on the liberation of gastro-intestinal or pancreatic hormones has also been suggested in several reports Thus dietary fibre has been demonstrated to influence postprandial rise in immunoreactive glucagon (10) GIP (11 14) and gastrin (14)

Long term beneficial effects of diets rich in dietary fibre have also been reported suggesting an increased peripheral sensitivity to insulin (for review see 7)

The present investigation deals with the effect of dietary fibre naturally occurring in normal food (i e the fibre was not added as an extra constituent in the meals) Two breakfasts with an almost identical content of digestible carbohydrates but differing in dietary fibre were given on different occasions to eight NIDD with continuous registration of postprandial plasma glucose levels (CGM apparatus, Gambro Lund Sweden)

PATIENTS AND METHODS

Patients

Six male and two female subjects with type II diabetes (NIDD) were included in the study Diabetes duration was at least one year Their mean ages and body mass indices (weight/height²) were 54 1 (±S D 8.6) years and 28.8 (±S.D 4 1). They were regular attenders at the Medical Clinic, Lund University Hospital None had detectable renal hepatic or endocrine disease apart from diabetes. All had conventional dietary regulation and none had received insulin or oral antidiabetic drugs

Each subject came in the fasting state to the outpatient clinic at 8.00 a.m on two occasions with an interval of at least one week

Test meals

Two breakfasts, A and B were prepared as shown in Table I The variation in dietary fibre content was obtained by selecting whole grain meal bread and whole apples in meal A and white bread and apple juice in meal B The amounts of the different food stuffs were selected to obtain the same amounts of absorbable carbohydrates in the two meals

One meal A and B was homogenized lyophilized and fat extracted with chloroform. The fat free powder was analyzed for digestible carbohydrates with enzymatic methods. Glucose and fructose was assayed with a

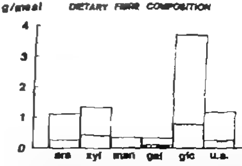

Fig 1 Composition of dietary fibre in the two test meals (A = open bars B = shaded bars), given as monosaccharide content after hydrolysis. ara = arabinose xyl = xylose man = manose gal = galactose glc = glucose and u.a. = uronic acids.

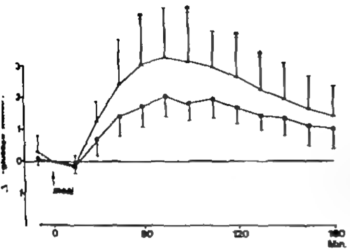

Fig. 2. Effect of breakfast rich (A, ●) and poor (B, ▲) in dietary fibre on blood glucose levels during three hours after ingestion of the meal. Expressed as changes (Δ B-glucose) from the fasting value. Mean and one S.E. indicated (*=$p<0.05$, **=$p<0.01$).

hexokinase-glucose-6-phosphate dehydrogenase system as described by Southgate (15). Galactose was assayed with galactose dehydrogenase (3). Sucrose and lactose were assayed by measuring glucose and galactose liberation after hydrolysis with purified β-fructosidase and β-galactosidase, respectively (Boehringer Mannheim). Starch was assayed as glucose increment after hydrolysis with amyloglucosidase (Boehringer Mannheim).

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Calculations

From the continuous blood glucose registrations the blood glucose increment from the fasting value after 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes were calculated. The time from the ingestion of the meal to the start of the plasma glucose rise, as well as the time when maximum blood glucose rise occurred, was measured. Statistical evaluation was performed with the Wilcoxon signed rank test.

RESULTS AND DISCUSSION

Test meal composition

As shown in Table II the content of glucose, fructose, sucrose, lactose and starch was almost identical in the two meals. The protein and fat content were also similar. The energy content was 1 660 KJ (398 kcal) and 1 600 KJ (383 kcal) respectively.

Breakfast A contained 3 times more dietary fibre than B (8.4 and 3.1 g respectively). The composition of the dietary fibre, given in Fig. 1, shows that the difference comprised pentosans (arabinose and xylose-based polysaccharides), cellulose and other glucose-based polysaccharides, as well as pectins (uronic acid-based polysaccharides).

Postprandial blood glucose curves

As shown in Fig. 2 the fibre rich meal (A) gave a smaller postprandial blood glucose increment than the corresponding low fibre meal (B). Differences in blood glucose rise were smaller at all intervals studied between 30 and 135 min ($p<0.05$ or <0.01). There was no difference in the mean time before blood glucose started to rise (21.9±4.6 min after meal A and 16.9±8.0 min after meal B). The mean time to maximum blood glucose rise was 96.9±27.9 and 81.3±21.3 min respectively. These values were also not significantly different.

In the present investigation we thus demonstrated a smaller blood glucose increment after a fibre rich breakfast meal compared with a low fibre meal with identical composition of the digestible carbohydrates. The difference seems to be due to the dietary fibre naturally occurring in the whole grain bread and the apple. Another contributing factor might be the lower degree of disruption of cells in the fibre rich meal.

Intact cell walls may function as barriers slowing down the enzymatic attack and thus decreasing intestinal absorption rate. Haber et al. (6) gave whole apples, apple purè, or apple juice to healthy volunteers demonstrating a higher insulin response with postprandial hypoglycemia after purè or especially juice, compared with the whole apples. Since

Table I *Composition (g) of breakfast meals with different dietary fibre content*

	A	B
Low fat (0.5%) milk	100	100
Cheese (28% fat)	25	25
Margarine (45% fat)	15	15
Whole grain wheat and rye bread	78	–
White wheat bread	–	75
Whole apple edible parts	100	–
Apple juice	–	100

Table II *Analysis of test meals (g/meal)*

	A	B
Protein	16.0	14.3
Fat	17.5	16.5
Glucose	1 6	1.6
Fructose	5 6	5.8
Galactose	<0 1	<0 1
Sucrose	2.1	2.1
Lactose	5 0	5.3
Starch	30 7	30.8
Dietary fibre	8.4	3 1
Energy*		
KJ	1 660	1 600
Kcal	398	383

Assuming no energy value of the dietary fibre

Addition of pectin and/or guar gum to meals or glucose solutions has been repeatedly shown to reduce postprandial plasma glucose and insulin in both healthy volunteers and diabetics Several authors have suggested that the improvement in glucose tolerance by these viscous fibres is due to slower absorption of the carbohydrate From some studies it has been concluded that this might be due both to a slower gastric emptying rate and to a slower small intestinal absorption (for review see 7) Others, however (8) have found evidence of an increased gastric emptying rate after addition of guar gum or bran

The possibility that dietary fibre influences glucose tolerance by more or less direct effects on the liberation of gastro-intestinal or pancreatic hormones has also been suggested in several reports Thus dietary fibre has been demonstrated to influence postprandial rise in immunoreactive glucagon (10) GIP (11 14) and gastrin (14)

Long term beneficial effects of diets rich in dietary fibre have also been reported suggesting an increased peripheral sensitivity to insulin (for review see 7)

The present investigation deals with the effect of dietary fibre naturally occurring in normal food (i e the fibre was not added as an extra constituent in the meals) Two breakfasts with an almost identical content of digestible carbohydrates but differing in dietary fibre were given on different occasions to eight NIDD with continuous registration of post prandial plasma glucose levels (CGM apparatus Gambro Lund Sweden)

PATIENTS AND METHODS

Patients

Six male and two female subjects with type II diabetes (NIDD) were included in the study Diabetes duration was at least one year Their mean ages and body mass indices (weight/height²) were 54 1 (±S D 8 6) years, and 28 8 (±S.D 4 1) They were regular attenders at the Medical Clinic Lund University Hospital None had detectable renal, hepatic or endocrine disease apart from diabetes. All had conventional dietary regulation and none had received insulin or oral antidiabetic drugs

Each subject came in the fasting state to the outpatient clinic at 8 00 a m. on two occasions with an interval of at least one week.

Test meals

Two breakfasts, A and B were prepared as shown in Table I The variation in dietary fibre content was obtained by selecting whole grain meal bread and whole apples in meal A, and white bread and apple juice in meal B The amounts of the different food stuffs were selected to obtain the same amounts of absorbable carbohydrates in the two meals.

One meal A and B was homogenized lyophilized and fat extracted with chloroform The fat free powder was analyzed for digestible carbohydrates with enzymatic methods Glucose and fructose was assayed with a

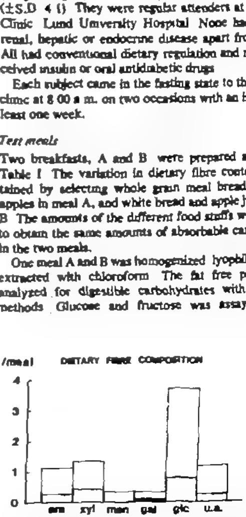
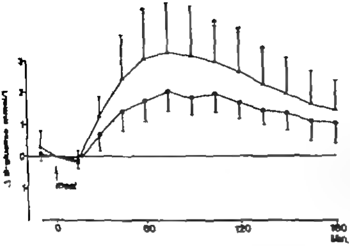


Fig 1 Composition of dietary fibre in the two test meals (A = open bars B = shaded bars) given as monosaccharide content after hydrolysis ara = arabinose xyl = xylose man = mannose gal = galactose glc = glucose and u.a. = uronic acids.



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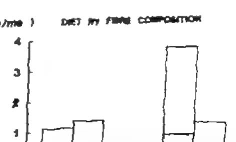

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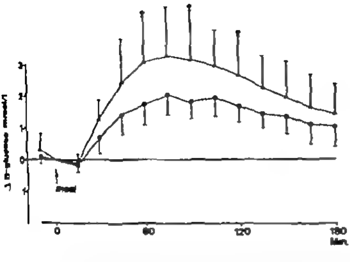

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RESULTS AND DISCUSSION

Test meal composition

As shown in Table II the content of glucose, fructose, sucrose, lactose and starch was almost identical in the two meals. The protein and fat content were also similar. The energy content was 1660 KJ (398 kcal) and 1600 KJ (383 kcal) respectively.

Breakfast A contained 3 times more dietary fibre than B (8.4 and 3.1 g respectively). The composition of the dietary fibre, given in Fig. 1, shows that the difference comprised pentosans (arabinose and xylose-based polysaccharides), cellulose and other glucose-based polysaccharides, as well as pectins (uronic acid-based polysaccharides).

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glucose fructose and sucrose are the main carbohydrates in apples this experiment also demonstrates that such low molecular weight carbohydrates may behave as "lente" carbohydrates when present in unprocessed fruits or vegetables

The difference in dietary fibre content between our two meals (5 3 g) is small compared to the doses of pectin or guar gum added to meals in other studies (usually 15–25 g) In another recent investigation however 6 6 g of Ispaghula fibre given as two doses of a bulk laxative (Lunelax®) to the breakfast meal to adult diabetics also gave a decreased plasma glucose response similar to that demonstrated in the present investigation (13) The Ispaghula fibre contains mainly arabinose and xylose-based pentosans

Analysis of immunoreactive insulin C-peptide glucagon and GIP are in progress Preliminary results indicate that insulin and C peptide levels were not significantly different after the two meals. Since glucose levels showed considerable differences the insulin/glucose ratio was obviously more favourable after the fibre rich meal

Further investigations are needed to dissolve the mechanism by which fibre rich meals improve glucose tolerance Effects on gastric emptying rate and intestinal absorption rate might be of importance and also effects on the release of gastro intestinal and pancreatic hormones Changes in peripheral insulin sensitivity must also be considered

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Acta Med Scand Suppl 656. 51–53 1981

Dietary Supplementation of Fibre (Lunelax®) as a Mean to Reduce Postprandial Glucose in Diabetics

Gunnar Sartor Sven Carlström and Bengt Scherstén

From the Department of Medicine University Hospital of Lund Lund Sweden

ABSTRACT The postprandial glucose concentrations after a standardized breakfast of 11 type II diabetics were followed and the effect of supplementation of fibre-containing bulk-purgative (Lunelax®) to the meal was investigated. It was found that addition of Lunelax® reduced the mean incremental glucose concentration with about 9%. The patients reported that Lunelax was convenient to take.

Several studies have been published during recent years concerning the effect of fibre addition to the diet of diabetics (1 2, 3 4 7). In most of the studies guar gum or pectin has been given and it has been shown that after addition of fibre postprandial glucose and insulin concentrations are reduced in diabetics both after a standardized meal and after glucose load (1 2). Furthermore, a reduction of the amount of glucosuria (3) and of given therapy both insulin and sulphonylureas, have been found (5). There is only one study in which no effect of fibre addition is found, but in this rather low dosage of guar gum and pectin has been used (7)

However in many of these studies the patients have reported of side effects with unpalatability abdominal discomfort and flatulence.

The aim of the present study was to find out whether fibre-containing bulk-purgative (Lunelax®) was able to reduce the postprandial glucose concentration in type II diabetics, treated with sulphonylurea drugs and dietary regulations

MATERIAL AND METHODS

Four women and eight men with mean age of 63 years (range 50–73 years) were selected for the study Eight of the patients were treated with chlorpropamide (Diabinese®), two with glibenclamide (Daonil®), one with glipizide (Mindiab®) and one with tolbutamide (Rastinon®). The mean weight of the patients was 72 kg and the mean weight index (percentage of ideal weight) was 116% (range 93–131%). None of the patients was given any other antidiabetic drug and none was on therapy with thiazides or corticosteroids. The patients were randomly divided into two groups, A and B At each examination the patients were given standardized breakfast meal including 400 ml low fat milk (containing 0.5% fat), two slices of white bread, 5 g of butter and 35 g cheese 150 ml black coffee without sugar This meal had an energy content of 1800 kJ (430 Kcal).

The blood glucose concentrations were determined before the breakfast meal and at 15, 30, 45 60, 75 90 and 120 min after Blood glucose was determined with the hexokinase method in the routine laboratory of Lund University Hospital. The patients were fasting since 10 p m. the night before the examination.

Every patient was examined at three occasions with an interval between the examinations of at least one week. The patients in group A were given Lunelax together with the test meal at the first and third examination, whereas only the test meal was given at the second examination. The patients in group B were given Lunelax plus the test meal only at the second examination. Lunelax was given in the dosage of 11 4 g, which contains 6 6 g of fibre. The patients in both groups thus served as their own controls.

Lunelax is bulk-purgative in powder containing Testa ispaghula, which is derived from the epidermis of the seeds of *Plantago ovata*. It consists of mixture of neutral and acid polysaccharides with rest of galacturonic acid. The polysaccharides are built up of the monomers D-xylose and L-arabinose and Testa ispaghula contains 67% pentosanes.

When it is mixed with water it forms jelly and should be drunk immediately

Lunelax® powder also contains 2.4 g lactose per 3.3 g Testa ispaghula and in order to test, whether the amount of lactose in the preparation influenced the blood glucose concentration, five healthy volunteers were given Lunelax in the fasting state in the morning. As shown in Fig 1 the mean blood glucose concentration was not found to be influenced.

The statistical evaluations were performed with Wilcoxon' rank sum test (6).

glucose fructose and sucrose are the main carbohydrates in apples this experiment also demonstrates that such low molecular weight carbohydrates may behave as "lente" carbohydrates when present in unprocessed fruits or vegetables.

The difference in dietary fibre content between our two meals (5.3 g) is small compared to the doses of pectin or guar gum added to meals in other studies (usually 15–25 g) In another recent investigation however 6 6 g of Ispaghula fibre given as two doses of a bulk laxative (Lunelax®) to the breakfast meal to adult diabetics also gave a decreased plasma glucose response similar to that demonstrated in the present investigation (13) The Ispaghula fibre contains mainly arabinose- and xylose-based pentosans

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The aim of the present study was to find out whether a fibre-containing bulk-purgative (Lunelax®) was able to reduce the postprandial glucose concentration in type II diabetics, treated with sulphonylurea drugs and dietary regulations.

MATERIAL AND METHODS

Four women and eight men with mean age of 63 years (range 50–73 years) were selected for the study Eight of the patients were treated with chlorpropamide (Diabinese®) two with glibenclamide (Daonil®), one with glipizide (Mindiab®) and one with tolbutamide (Rastinon®) The mean weight of the patients was 72 kg and the mean weight index (percentage of ideal weight) was 116% (range 93–131%). None of the patients was given any other antidiabetic drug and none was on therapy with thiazides or corticosteroids. The patients were randomly divided into two groups, A and B. At each examination the patients were given standardized breakfast meal, including 400 ml low fat milk (containing 0.5% fat) two slices of white bread, 5 g of butter and 30 g cheese 150 ml black coffee without sugar This meal had an energy content of 1800 kJ (430 Kcal)

The blood glucose concentrations were determined before the breakfast meal and at 15 30, 45 60, 75 90 and 120 min after Blood glucose was determined with the hexokinase method in the routine laboratory of Lund University Hospital The patients were fasting since 10 p.m. the night before the examination

Every patient was examined at three occasions with an interval between the examinations of at least one week. The patients in group A were given Lunelax® together with the test meal at the first and third examination, whereas only the test meal was given at the second examination The patients in group B were given Lunelax plus the test meal only at the second examination. Lunelax was given in the dosage of 11 4 g, which contains 8 6 g of fibre. The patients in both groups thus served as their own controls.

Lunelax is bulk-purgative in powder containing Testa ispaghula, which is derived from the epidermis of the seeds of *Plantago ovata*. It consists of mixture of neutral and acid polysaccharides with rest of galacturonic acid. The polysaccharides are built up of the monomers D-xylose and L-arabinose and Testa ispaghula contains 67% pentosanes

When it is stirred with water it forms jelly and should be drunk immediately

Lunelax powder also contains 2.4 g lactose per 3.3 g Testa ispaghula and in order to test, whether the amount of lactose in the preparation influenced the blood glucose concentration, five healthy volunteers were given Lunelax in the fasting state in the morning. As shown in Fig. 1 the mean blood glucose concentration was not found to be influenced.

The statistical evaluations were performed with Wilcoxon rank sum test (6).

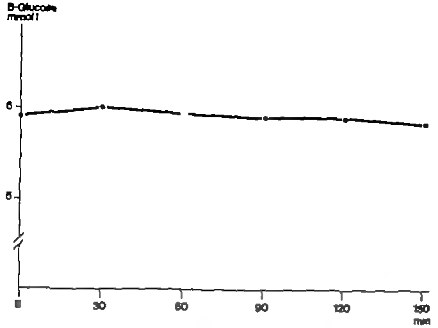

Fig 1 Mean blood glucose concentration of 5 healthy volunteers after intake of 11 4 g Lunelax®

RESULTS

The mean blood glucose curves of the two groups are given in Fig 2 The mean fasting blood glucose concentration was the same in both groups when the standardized meal was given with and without Lunelax® When the patients were given Lunelax® together with the breakfast the glucose increment above base-line was lower than without Lunelax® Furthermore the peak of the curve occurred later when Lunelax was given Fig. 3 shows the mean blood glucose concentrations with and without Lunelax® added to the test meal when the results of the two groups are pooled.

In average the peak concentration was reduced

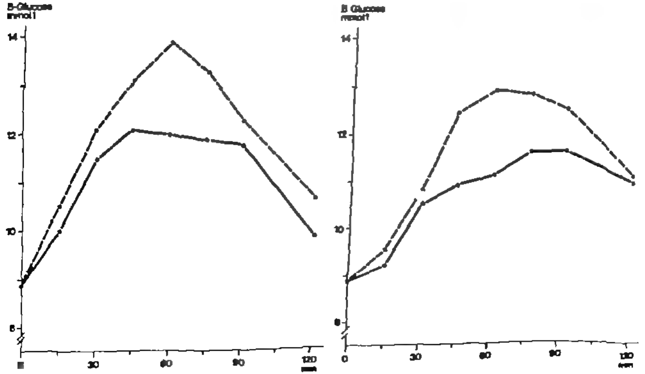

Fig 2 Mean blood glucose concentrations of group A (left) and B (right) with (unbroken line) and without (broken line) Lunelax® added to the standardized breakfast.

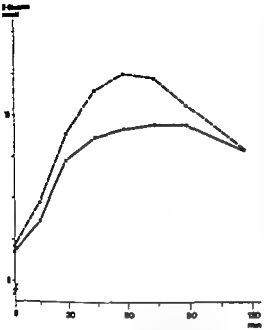

Fig. 3 Mean blood glucose concentration (groups A and B pooled) with (unbroken line) and without (broken line) Lunelax added to the standardized breakfast meal

th 9% when Lunelax® was given together with the test meal. The differences between the blood glucose increments were significant from 30 min up to 60 min after the breakfast meal (p less than 0.05)

None of the patients had any inconvenience of the examinations and they reported that the powder was acceptable to take in, when drunk immediately after the mixture with water

DISCUSSION

Judging from our results, it was possible to reduce the postprandial glucose concentration when Lunelax was added to the meal. Assuming the hypothesis that peaks in the blood glucose concentration of even short duration may lead to secondary diabetic complications due to the intracellular sorbitol pathway it must be of value to reduce the blood glucose increments. The effect of dietary fibre on the glucose curve may be due partly to a delayed emptying of the stomach and partly to a delayed absorption of glucose From other studies with guar gum as the dietary fibre it is known that above the glucose-reducing effect of the fibre *per se* the viscosity of the preparation also plays a role (4)

The Lunelax® powder was acceptable to take in, which gives it an advantage in comparison with guar gum and pectin. This observation is confirmed by the fact that patients suffering from obstipation, had taken in through many years in higher daily dosages. Another advantage may be that it is available in small bags containing 5 7 g of the powder (3.3 g fibre) and thus it is convenient for the patients to get the right dosage.

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Acta Med Scand, Suppl 656. 55–57 1981

Oral Antidiabetic Therapy

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The currently available drugs for oral treatment of type II diabetes are of two kinds, sulfonylureas (SU) and biguanides (BG). Although the knowledge of their effects is far from complete, it can be stated with certainty that their mechanisms of action are entirely different Most importantly SU has virtually no blood glucose reducing effect unless some B-cell function still persists whereas BG can diminish the blood glucose levels even in patients without any insulin production.

From the practical point of view the major issue is the balance between therapeutic efficiency and the risk of serious adverse reactions. There is increasing reason to admit that the effect of BG is less well understood, less physiological and more harmful than that of SU Therefore this presentation concentrates on the clinical pharmacology and therapeutics of SU

The UGDP study inferred that the long-term treatment with SU was harmful rather than beneficial (11). However subsequent analyses of the UGDP study have suggested that the UGDP claims are invalid (13 14). Moreover recent long-term studies indicate that SU may be highly beneficial indeed, SU may be capable of preventing or postponing the development of impaired glucose tolerance to manifest diabetes (5 6) This leads the authors to the standpoint that SU is a valuable therapeutic aid but that its use should be more appropriate

By the above reasoning, the following question emerges. What is the appropriate use of SU In addition, are there major differences between different SU preparations In an effort to answer these questions a series of studies has been carried out in both diabetic patients and healthy volunteers, including not only pharmacodynamic but also pharmacokinetic aspects. The results and conclusions can be summarized as follows.

Effect of SU

It is generally agreed that SU can stimulate the secretion of insulin from the B-cells. However it is a matter of debate whether SU can lower blood glucose also via extrapancreatic effects. Indirect evidence for such an influence has been obtained from single-dose studies in volunteers. Oral administration of 0.5 g tolbutamide was found to reduce blood glucose within such a brief time that the peripheral plasma concentration of the drug still was close to zero Moreover there was no measureable increase of peripheral plasma insulin Thus, although the peripheral venous concentration—and hence the pancreatic concentration—of tolbutamide had not yet reached the level necessary to trigger insulin release the entrance of the drug into gastrointestinal tract evoked a reduction of blood glucose Presumably this reflects an influence of SU on hepatic output of glucose, either by a direct effect or via interference with the hepatic disposition of insulin (7)

Another possible explanation of the above-mentioned phenomenon may be that the entrance of SU in the gastrointestinal tract promotes secretion of duodenal insulin-releasing activity (DIRA). Evidence for such an influence has been presented by others (15) and additional support in favour of this idea has recently been obtained in diabetics treated with glipizide in two different ways. (*a*) the whole daily dose of glipizide (15 mg) was given before breakfast; (*b*) the same dose was fractionated as 5 mg before breakfast, lunch and dinner The former treatment led to very high concentrations of glipizide in peripheral blood not only during breakfast time but also during lunch time. Indeed the glipizide concentrations at lunch time were higher after the former than after the latter treatment, in spite of the second 5 mg glipizide dose taken before lunch during the latter regimen. Nevertheless, the

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lunch dose of glipizide promoted a greater C-peptide and insulin increase and a more pronounced glucose reduction after lunch than seen following lunch during the 15 mg once daily regimen Reasonably the improvement can hardly be due to glipizide reaching the pancreas via systemic circulation but rather to the appearance of glipizide within the gastrointestinal tract (1)

Another extrapancreatic effect of SU is also suggested by the above-cited study (1) It was found that even though the glipizide concentration after breakfast was much higher on the 15 mg once daily regimen than on 5 mg thrice daily the C peptide responses to breakfast were essentially identical However the former treatment yielded 60–70% more insulin in peripheral blood than the latter regimen It seems reasonable to assume that this was due to an altered extrapancreatic disposition of the insulin released from the pancreas (1) A possible additional mechanism is that sulfonylureas may enhance the number or reactivity of insulin receptors (16 17)

To summarize SU may enhance insulin secretion not only by direct stimulation of the B-cell but also directly via an influence on the secretion of duodenal insulin-releasing activity In addition SU may alter the extrapancreatic disposition of the insulin released Moreover SU may influence insulin receptors. As recent studies have shown that SU may affect the secretion of not only insulin but also of glucagon (3) somatostatin (2) and gastrin (12) it is obvious that the influence of SU on the regulation of glucose economy is very complex

Individualization of SU dosage

Studies on the steady state concentrations and effects of tolbutamide and chlorpropamide in diabetic patients treated with either drug for at least one year showed that the fasting blood glucose concentrations were normal in very few cases and that they were below 8 mmol/l in less than half of the patients One of the presumably several reasons for this therapeutic insufficiency is to be sought in the fact that the steady state concentrations of the two SU drugs varied extensively between patients Indeed the chlorpropamide concentrations showed an interindividual range from close to zero to above 800 μmol/l Part of the explanation for this phenomenon is probably bad compliance with therapy but it is also likely that interindividual differences in the absorption metabolism and excretion of the drugs are important (4)

Irrespective of the mechanism involved the findings support the view that the dosage of tolbutamide and chlorpropamide should be more individualized than is currently practised (4). Subsequent studies on glibenclamide (8) and glipizide (unpublished data) indicate that the same is true also for these two SU drugs.

Difference between SU drugs

In an attempt to assess quantitative differences between different SU drugs the single-dose kinetics and effects of tolbutamide (500 mg) chlorpropamide (250 mg) glibenclamide (5 mg) and glipizide (5 mg) were studied in healthy volunteers. The findings indicated that even though the plasma concentrations of glibenclamide and glipizide were only about 1/1000 of those of tolbutamide and chlorpropamide they exerted more pronounced blood glucose reductions than the two older drugs. Thus the intrinsic activity of glibenclamide and glipizide is much greater than that of tolbutamide and chlorpropamide (9)

As far as possible differences between glipizide and glibenclamide are concerned the former evoked a more pronounced insulin increase and a deeper blood glucose reduction than the latter However this difference may at least in part be due to pharmacokinetic differences the bioavailability of glipizide from its preparation used was obviously greater than that of glibenclamide from its preparation (9)

Relation between intake of SU and intake of meals

As an adequate dietary regulation is of utmost importance in the treatment of diabetes it also seems urgent to establish appropriate relations between the intake of SU and the ingestion of meals. To this end the influence of a standardized breakfast on the kinetics and effects of a single-dose of glipizide (5 mg) was studied both in healthy volunteers and in diabetic patients. It was found that food intake can delay the absorption of glipizide by approximately ½ hour probably by delayed gastric emptying Administration of the drug ½ hour before breakfast was found to yield significant amounts of the drug in peripheral blood at the time of breakfast start whereas concomitant administration of drug and breakfast did not yield assumed therapeutic con-

centrations until at least ½ hour after breakfast start. It was also seen that administration of the drug before breakfast yielded a significantly greater blood glucose reduction than did concomitant administration of drug and meal. This could be related to differences in the temporal pattern of insulin secretion, signifying that administration of the drug before breakfast yielded a more appropriate relation between the carbohydrate load of the meal and insulin release (10).

Subsequent studies on glibenclamide indicate that, even though food apparently does not influence the kinetics of this drug (8), administration of the drug ½ hour before breakfast may enhance the blood glucose reduction in response to treatment (18). Thus, it seems justified to suggest that the therapeutic effect of both glipizide and glibenclamide may be improved by administration of the drugs ½ hour before meals rather than together with meals.

Conclusions

The knowledge about the pharmacodynamics of SU is far from complete. It appears that SU may enhance insulin secretion both directly and indirectly and that SU also may alter the extrapancreatic disposition of insulin released from the B-cells. As SU in addition may influence the secretion of other gastrointestinal hormones, their influence on glucose economy is very complex. The dosage of SU should always be individualized. The greater potency of glipizide and glibenclamide as compared to first-generation SU such as tolbutamide and chlorpropamide may offer a therapeutic advantage. The therapeutic effect of both glipizide and glibenclamide may be improved if the drugs are ingested ½ hour before meals rather than together with meals.

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Acta Med Scand, Suppl. 656. 59–61 1981

Determination of Hemoglobin A_{1C} in Diabetic Patients

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There is growing evidence that improved diabetes regulation will decrease the rate of development of later complications. To improve regulation new tools have been developed, in addition to the common combination of fasting blood glucose and 24 h urine glucose a few times every year Glycosylated hemoglobin (HbA_{1C}) reflects the mean blood glucose concentrations during the preceding 3–5 weeks, and thus periodic determination of HbA_{1C} means a very valuable tool for monitoring diabetes care (1 2) The glycosylated HbA_{1C} is a postsynthetic modification of HbA and has the same amino acid sequence and 1-amino-1-deoxyfructose group covalently bound to the N-terminal amino acid in the beta chains (3) The rate of this nonenzymatic reaction is dependent on the glucose concentration in the blood In normal individuals HbA_{1C} constitutes about 7% of the total hemoglobin.

The HbA_{1C} fraction can be separated from the major fraction by several methods. The original ion exchange chromatography method by Trivelli (4) has been replaced by several commercial microcolumns. Although simple to operate there are major drawbacks with these methods. The reproducibility is strongly temperature dependent and the columns may vary from batch to batch (5). Not only HbA_{1C} but also minor hemoglobins, HbF including artifacts caused by storage of the test samples will be lumped together and the results may be unreliable Among the other methods high pressure liquid chromatography (6) and colorimetric methods (7) have been reported as well as electrofocusing procedure (8).

We report here the use of an improved electrofocusing technique to determine HbA_{1C} in diabetics and we compare the results with simultaneously taken sample for fasting blood glucose

MATERIALS AND METHODS

Adult diabetics had fasting blood sample taken for glucose and HbA_{1C} Glucose was analysed with the hexokinase method.

HbA_{1C} The blood was collected in EDTA containing tubes. 1 ml whole blood was mixed with 10 ml isotonic saline and the supernatant was discarded after 5-min centrifugation at 3000 g T induce hemolysis, 6 ml of 0.01 M KCN solution plus 3 drops of CCl were added to the washed red cells. The clear supernatant after centrifugation was now free of stroma, and the hemoglobin concentration approximately 20 g/l.

Home-made (8) or ready-made polyacrylamide gels (PAG-plates 1804-131) LKB-Produkter AB S-16125 Bromma, Sweden) was used, and the electrofocusing was performed in the LKB 2117 Multiphor apparatus with constant power supply LKB No 2103 Water was circulated 5–10 l/min at 15°C through the cooling plate. Filter paper at the cathodal end was moistened with 0.1 M NaOH and for the anodal end with 0.04 M glutamic acid. The gels were prerun for 30 min at 2000 V 20 W and 50 mA maximum, and then 15 µl of hemolysate was applied on 5 10 mm filter papers on the gels. These filter papers were removed after 40 min with the same electrical setting. After another 70 min the power was increased to 30 W for further 10 min. The optimal gel temperature is 18–20°C

Afterwards, the gel containing the HbA_{1C} fractions were cut out using thin scalpel blade and transferred to 1 ml of elution buffer 0.05 M Tris HCl and 0.1 mM EDTA, pH 8.3 Previously 15 µl of the same hemolysate had been transferred to 5 ml of the eluting buffer The tubes were sealed and mounted on rocking table in 4–10°C over night The percentage HbA_{1C} was determined as the absorbance at 415 nm compared to absorbance of total hemoglobin. Every 10th sample was control from pool of healthy donors.

RESULTS AND DISCUSSION

There was a relatively low (0.56) correlation between % HbA and fasting blood glucose for insulin-treated patients (Fig. 1). This is not surprising since a random blood glucose—fasting or postpran-

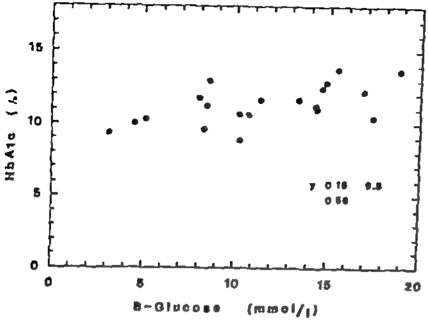

Fig 1 Correlation between HbA_{1c} and B-glucose for insulin-treated patients

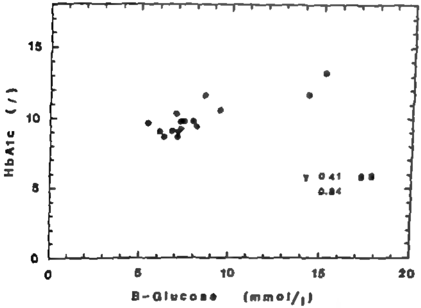

Fig 2 Correlation between HbA_{1c} and B-glucose for patients on tablet or diet regime.

dial—is relevant only for a very short period of the sampling day while HbA_{1c} reflects the mean glucose level during several weeks This speaks in favour of the regular blood glucose testing being transferred to the task of the patients to get profiles over the day to study the balance between food intake exercise and medication On the other hand HbA_{1c} will be valuable to the physician to get an overview of the grade of regulation not depending on the notes of the patients

However the patients with tablet or diet regime showed a very high correlation (0 84) between HbA_{1c} and B-glucose (Fig 2) This indicates that HbA_{1c} determinations can be devoted to insulin-treated patients with a wider range in the blood sugar level.

The introduction of HbA_{1c} in the routine tests of insulin-treated diabetics seems to be justified. It does not rule out the random blood glucose determination but these tests might be more efficiently used in the hands of patients—after adequate information—than a periodic single blood glucose value would do in the hands of the physician It is our experience since several years that many patients get less frustrated and much more interested in their own management of diabetes with the use of

simple blood glucose tests (Reflotest, Dextrostix with photometer BM Test Glycemie 1–44) than with testing of the urine. The profiles demonstrated in these tests are helpful to explain what changes have to be done in the daily care. Determination of HbA_{1c} with a reliable and reproducible method, that can be easily arranged in most hospital laboratories, will in the future give the physician a very good index of the grade control during an extended period. The method must have a good precision and accuracy because of the rather small range of HbA_{1c} values.

Very recent results show that the specificity can be further improved by incubation of red cells in saline to eliminate a reversible fraction that will influence on the true HbA_{1c} level (9). This fraction is visible on isoelectric focusing anodal to the HbA_{1c}-fraction.

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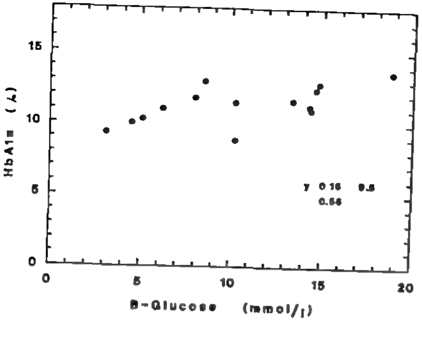

Fig 1 Correlation between HbA_{1c} ... B-glucose for insulin-treated patien...

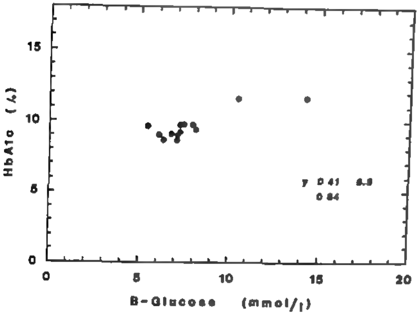

Fig 2 Correlation between HbA_{1c} a... B-glucose for patients on tablet or di... regime.

dial—is relevant only for a very short period of the sampling day while HbA_{1c} reflects the mean glucose level during several weeks This speaks in favour of the regular blood glucose testing being transferred to the task of the patients to get profiles over the day to study the balance between food intake exercise and medication On the other hand HbA will be valuable to the physician to get an overview of the grade of regulation not depending on the notes of the patients

However the patients with tablet or diet regime showed a very high correlation (0 84) between HbA_{1c} and B-glucose (Fig. 2) This indicates that HbA_{1c} determinations can be devoted to insulin-treated patients with a wider range in the blood sugar level

The introduction of HbA in the routine tests of insulin-treated diabetics seems to be justified It does not rule out the random blood glucose determination but these tests might be more efficiently used in the hands of patients—after adequate information—than a periodic single blood glucose value would do in the hands of the physician It is our experience since several years that many patients get less frustrated and much more interested in their own management of diabetes with the use of

Acta Med Scand, Suppl. 656: 63–67 1981

Hemoglobin A_1 in Community Care

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ABSTRACT In order to investigate the potential usefulness of knowing the blood concentrations of HbA_1 in primary care, HbA_1 was measured in diabetic subjects attending a primary care centre. The values were compared with concentration of HbA in a reference group on non-diabetics. The reference group had a mean value in HbA_1 of 7.6 ± 0.1 % with a tendency to increased values with advancing age. The diabetic subjects had a mean value in HbA_1 of 10.8 ± 0.2 %. Diabetics under good control had lower values (10.2 ± 0.2 %), than patients under poor control (12.0 ± 0.2 %) ($p < 0.001$). There was a correlation ($r = 0.50$, $p < 0.001$) between HbA_1 and fasting blood glucose levels. It is concluded that determination of HbA_1 can be an aid in the control of diabetics in primary care. However the method requires good technical management, and the results are most reliable when the same person analyses all samples. The objective in diabetic therapy in this respect should no doubt be to depress the concentrations of HbA_1 towards normal values.

Key words Hemoglobin A_1, fasting blood glucose clinical evaluation, diabetics, non-diabetics, primary care.

The nature and degree of control of the diabetic patient is still a controversial question (5 8 34) The care of the patient has as its aim to lead not only to the absence of symptoms, but also to the prevention of long-term complications. Most studies suggest that certain complications can be at least delayed by improving the metabolic control (18, 21). Nevertheless, there is a lack of suitable methods for assessing this metabolic control The degree of metabolic control has to be considered in relation to a period of time rather than to certain point of time. Certain parameters such as urinary glucose excretion or blood glucose concentration can be used in order to choose the correct type of treatment. The development of a method for determining glycosylated hemoglobins, HbA_1 an indicator of the plasma glucose level during the last 2–3 months, is aimed at evaluating the degree of control (15, 24).

In this study HbA_1 was determined in 156 consecutive diabetics attending a community care centre and in a reference population of non-diabetics at the same centre. Furthermore the HbA_1 concentrations were correlated to fasting blood glucose levels and to a clinical evaluation of the patient. The aim of the study was to establish the possibility of integrating determinations of HbA_1 in the practical care of out-patient diabetics at a primary care centre.

STUDY POPULATION AND METHODS

The study was performed at the community care centre in Dalby near Lund, Sweden At this centre all diabetics not treated by pediatricians attend a special diabetic unit run by a specially trained nurse educated in diabetic care. The diabetic unit is integrated in the regular community care Thus each physician at the community care centre has his own patients also among the diabetics. This system of diabetic care offers the great advantage of a very close personal knowledge of all patients and a high degree of continuity Moreover it offers a good educational situation in diabetology at this community care centre.

A total of 156 diabetic patients consecutively attending the diabetic unit during a 3-month period, were included in the study The mean age was 67.0 ± 1.2 years (*M* ± S.E.M.) Of the patients 63 (40 %) were treated with insulin, 60 (39 %) with oral hypoglycemic agents, and 33 (21 %) with diet alone.

The reference group consisted of 66 patients, consecutive patients at the community care centre during 2 days. They were non-diabetics.

The degree of diabetic control was evaluated by the nurse who beside anamnestic information and the physical investigation, also had knowledge of actual and earlier blood glucose levels. She also had a good knowledge of the patient and the patient's self control but no knowledge about concentrations of HbA_1. The degree of clinical control was classified as being good, satisfactory or poor

Concentrations of blood HbA_1 were measured with ion exchange chromatography at 22°C and pH 6.7 according to Trivelli (35) with the commercially available kit Bio-Rad Hemoglobin A_1 test® from Bio-Rad Laboratories, Richmond, California, USA. Blood glucose was determined by a hexokinase method (Boehringer Mannheim Gmbh, Mannheim, FRG). Means and standard errors of the mean are given.

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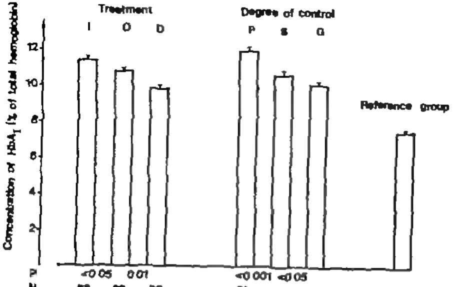

Fig 1 Blood concentrations of hemoglobin A_1 (% of total hemoglobin) in the different groups of diabetic subjects compared with that in the reference group Bars indicate S.E.M P probability level of random difference between groups *N* number of subjects in each group *I* insulin treatment *O* treatment with oral hypoglycemic agents, *D* treatment with diet only *G* good degree of control *S* satisfactory degree of control and *P* poor degree of control, respectively

RESULTS

HbA_1 in the reference group

The 66 non-diabetic patients in the reference group had a mean blood concentration of HbA_1 of 7 6±0 1% (M ± S E M) Patients over 45 years of age had higher HbA_1 concentrations 8 0±0 1% (n=39) whereas those below 45 had lower HbA_1 concentrations 7 2±0 1% (n=27) (p<0 001). Blood glucose values were 4 7±0 1 mmol/l with no age dependence

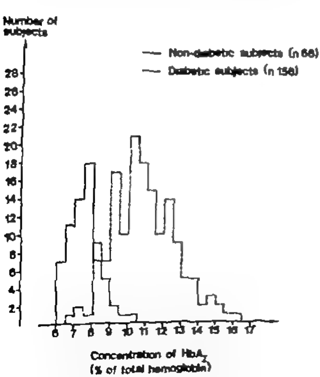

Fig 2 Distribution profiles in blood concentrations of hemoglobin A_1 for the diabetic population and the reference group respectively *Number of subjects is indicated as a function of the concentrations in HbA_1*

HbA_1 in the diabetic group

According to the clinical examination of the diabetic patients 75 (48%) were considered as being under a good diabetic control whereas 30 (19%) was under satisfactory control and 51 (32%) poorly controlled The concentration of HbA_1 in the diabetic group as a whole was 10 8±0 1% (p<0 01 vs. the reference group) Fig 1 shows the values of HbA_1 in the various groups according to treatment as well as degree of control It is seen that patients with a good degree of control had lower HbA_1 values than the others and that poorly controlled patients as a group had the highest HbA_1 values Fig 1 *also shows that insulin-treated patients had the* highest and patients treated with diet alone the lowest *concentrations of HbA_1*

Fig. 2 shows the distribution of the patients related to the distribution of the reference group with regard to HbA It is seen that the two populations slightly overlapped each other in this respect but the diabetics as a group had higher HbA values

Fasting blood glucose

Table I sets out the fasting blood glucose in the various subgroups of diabetics. *It is seen as expected* that the highest values were determined in *patients with a poor degree* of control in conformity with the fact that blood glucose levels were one of the aids used to assess the degree of control Fig

Table I. *Mean concentrations of hemoglobin A (% of total hemoglobin) and fasting blood glucose (mmol/l) in the diabetic subjects as a function of degree of control and treatment respectively*

n indicates number of subjects

Degree of control	Treatment							
	Insulin		Oral hypoglycemic agents		Diet only		Total	
	HbA_1	Glucose	HbA_1	Glucose	HbA_1	Glucose	HbA_1	Glucose
Good	10.6 [illegible]	4.9 7	10.2 n=28	5.7 n=14	9.7 n=25	5.3 n=13	10.2 n=75	5.4 n=34
Satisfactory	11.1 13	7.4 n=6	10.6 n=13	7.5 n=8	10.1 n=4	7.2 n=3	10.7 n=30	7.4 n=17
Poor	12.3 n=28	11.3 16	11.9 n=19	10.2 n=13	10.6 n=4	9.4 n=2	12.0 n=51	10.6 n=31
Total	11.4 n=63	9.0 n=29	10.8 n=60	7.8 n=35	9.9 n=33	6.2 n=18	10.8 n=156	7.8 n=82

3 shows the correlation between fasting blood glucose and HbA_1 for the whole diabetic group. The correlation between fasting blood glucose and HbA_1 was low although significant, the correlation coefficient ( ) being 0.50 ($p<0.001$).

DISCUSSION

It has long been known that protein-bound carbohydrate levels are elevated blood samples from diabetics (4) and it has been suggested that a deranged metabolism of such proteins might be of etiological significance for the development of long-term complications (12, 31). Tissues which are insulin-independent for their glucose uptake, e.g. erythrocytes, retina, neural structures and the kidney, have high intracellular glucose levels in deranged diabetes. This high intracellular glucose concentration may, by several mechanisms, influence metabolic pathways. This is presumed to be followed by the development of disturbed functions in these tissues (1, 3, 7, 14, 22, 30, 36) and later to diabetic complications. One such mechanism is the non-enzymatic glycosylation of proteins (1, 7, 22, 30). Thus, measurement of these proteins might be of use in the care of diabetics, with special regard to development of complications.

This idea has been stimulated by the discovery of HbA_1 (1) which is hemoglobin glycosylated through an irreversible post-synthetic, non-enzymatic process occurring in proportion to the blood glucose concentration (15, 24). Since the process is irreversible, high HbA_1 levels will persist for a quite long period of time. Thus the HbA_1 concentration might serve as an indicator of the integrated blood glucose during this time.

HbA_1 can be subdivided by chromatographic methods in several subfractions named HbA_{1a1}, HbA_{1a2}, HbA_{1b}, HbA_{1c}, HbA_{1d} and HbA_{1e}. Various carbohydrates are bound to the different forms of HbA_1, which probably cause the chromatographic

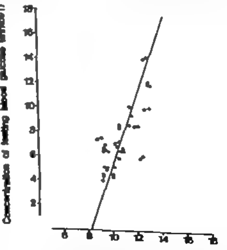

Fig. 3. Correlation between blood concentrations of fasting glucose (mmol/l), and hemoglobin A_1 (% of total hemoglobin) among 82 diabetic patients. Each point indicates one patient. The regression line ($y=3.3x-22.4$) was calculated according to the least square method.

discrepances (15 24) Presumably HbA_{Ic} is of importance in diabetes since the carbohydrate bound to this HbA_I is glucose (6) In the present study total HbA_I was *measured The methods for discriminating the different forms of* HbA_I are more complicated than the ion exchange chromatography used here and these complicated methods are still difficult to handle for the laboratory in primary care (cf 10 19 20) Furthermore, the fraction of HbA_I consisting of other minor hemoglobins than HbA_{Ic} *are rather small and probably do not affect interpretation* of the results when measuring total HbA_I (15 24) Moreover a good correlation between total HbA_I and other parameters used for assessing the degree of metabolic control in diabetes such as post-prandial glucose levels (2) mean blood glucose during a longer period (9) glycosylated serum proteins (30) or *protein-bound hexoses (22) have been* reported Ion exchange chromatography however requires a very good technical management and the values are most reliable when the same person analyses all samples In addition resin chromatography is very temperature dependent, and if the temperature in the laboratory varies the measured HbA_I values must be corrected Taken together however it is easier to introduce determinations of HbA_I than of HbA_{Ic} in primary care and the advantage of knowing HbA_{Ic} rather than total HbA_I does not balance the difficulties of introducing *complicated methods at the routine laboratory* A methodological improvement may perhaps lead to an easier estimation of HbA_{Ic} in the future It could be mentioned that also other minor hemoglobins than HbA_{Ic} may be elevated in diabetes (11) and some *information may thus be missed when determining* HbA_{Ic} only

Ion exchange chromatography makes it possible to integrate knowledge of glycosylated hemoglobins in the primary care of out patient diabetics Earlier studies have shown *values for HbA in normal subjects* to be 5–8.5% (2, 26 28 32 35) and HbA_{Ic} to be 3–5% (28 32 35) Diabetics have been reported to have mean HbA_{Ic} concentrations of 5–14% (2, 9 26 28 32 35) with a high correlation to the degree of control (2 9) *The present study shows* HbA_I for a diabetic population in primary care and the results tally with these earlier results on other diabetic populations The diabetics in our study had a mean HbA_I of 10 8% and the distribution of HbA slightly overlapped that in the *reference group* Patients treated with insulin had higher HbA_I and as expected those with a clinically poorly controlled diabetes likewise had high values of HbA_I

We find a correlation between HbA_I and fasting blood glucose A higher degree of correlation to HbA_I has been noted for post-prandial blood glucose levels (2) *the response to an oral glucose load* (23 26) urinary glucose excretion (17 27) and to mean glucose levels over a longer period (9 16 25). Thus the correlation is highest between HbA_I and parameters which are most closely connected to the *degree of long-term metabolic control* It may be discussed to what value HbA_I ought to be depressed in diabetics According to the results seen in Fig. 3 it may be speculated that values lower than 8-9% might be difficult to obtain in diabetics since the regression line intercepts the abscissa at 8.3% However since the glycosylation of hemoglobin is *proportional to blood sugar concentrations* it cannot be excluded that values seen in the reference groups should be the aim for HbA_I also among diabetics.

In conclusion the present study has shown that it is possible to introduce determinations of HbA_I in clinical practice in primary out patient care of diabetics *Since the measurement of* HbA_I is an objective analysis independent of the acute situation relation to food intake physical work patient compliance and time of day it can be used in relation to the objective of treatment for each individual *However the value of* HbA_I must be integrated with other aids for care of the patient A high level of HbA_I shows that the control is unsatisfactory but does not indicate how to improve it. Here we still need knowledge about the patient and the disease and *participation of the patient* his family the diabetic team and society at large A high degree of care continuity diabetic units and a high degree of patient education and motivation are still of the utmost importance in diabetic care

ACKNOWLEDGEMENT

The skilful assistance of Hannelore Claesson and Madeleine Svensson is gratefully acknowledged.

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discrepances (15 24) Presumably HbA_{Ic} is of importance in diabetes since the carbohydrate bound to this HbA_I is glucose (6) In the present study total HbA_I was measured The methods for discriminating the different forms of HbA_I are more complicated than the ion exchange chromatography used here and these complicated methods are still difficult to handle for the laboratory in primary care (cf 10 19 20) Furthermore, the fraction of HbA_I consisting of other minor hemoglobins than HbA_{Ic} are rather small and probably do not affect interpetation of the results when measuring total HbA_I (15 24) Moreover a good correlation between total HbA_I and other parameters used for assessing the degree of metabolic control in diabetes such as post prandial glucose levels (2) mean blood glucose during a longer period (9) glycosylated serum proteins (30) or protein-bound hexoses (22) have been reported Ion exchange chromatography however requires a very good technical management and the values are most reliable when the same person analyses all samples In addition resin chromatography is very temperature dependent and if the temperature in the laboratory varies the measured HbA_I values must be corrected Taken together however it is easier to introduce determinations of HbA_I than of HbA_{Ic} in primary care and the advantage of knowing HbA_{Ic} rather than total HbA_I does not balance the difficulties of introducing complicated methods at the routine laboratory A methodological improvement may perhaps lead to an easier estimation of HbA_{Ic} in the future. It could be mentioned that also other minor hemoglobins than HbA_{Ic} may be elevated in diabetes (11) and some information may thus be missed when deter mining HbA_{Ic} only

Ion exchange chromatography makes it possible to integrate knowledge of glycosylated hemoglobins in the primary care of out patient diabetics. Earlier studies have shown values for HbA_I in normal subjects to be 5–8.5% (2, 26 28 32, 35) and HbA_{Ic} to be 3–5% (28, 32 35) Diabetics have been reported to have mean HbA_{Ic} concentrations of 5–14% (2, 9 26 28 32, 35) with a high correlation in the degree of control (2, 9) The present study shows HbA for a diabetic population in primary care and the results tally with these earlier results on other diabetic populations The diabetics in our study had a mean HbA_I of 10 8% and the distribution of HbA_I slightly overlapped that in the reference group Patients treated with insulin had higher HbA_I and as expected those with a clinically poorly controlled diabetes likewise had high values of HbA_I

We find a correlation between HbA_I and fasting blood glucose A higher degree of correlation in HbA_I has been noted for post-prandial blood glucose levels (2) the response to an oral glucose load (23 26) urinary glucose excretion (17 27) and to mean glucose levels over a longer period (9 16 25) Thus the correlation is highest between HbA_I and parameters which are most closely connected to the degree of long-term metabolic control It may be discussed to what value HbA_I ought to be depressed in diabetics. According to the results seen in Fig 3 it may be speculated that values lower than 8–9% might be difficult to obtain in diabetics since the regression line intercepts the abscissa at 8 3% However since the glycosylation of hemoglobin is proportional to blood sugar concentrations it can not be excluded that values seen in the reference groups should be the aim for HbA_I also among diabetics

In conclusion the present study has shown that it is possible to introduce determinations of HbA_I in clinical practice in primary out patient care of diabetics Since the measurement of HbA_I is an objec tive analysis, independent of the acute situation relation to food intake physical work patient compliance and time of day it can be used in relation to the objective of treatment for each individual However the value of HbA_I must be integrated with other aids for care of the patient A high level of HbA_I shows that the control is unsatisfactory but does not indicate how to improve it. Here we still need knowledge about the patient and the disease and participation of the patient, his family the diabetic team and society at large. A high degree of care continuity diabetic units and a high degree of patient education and motivation are still of the utmost importance in diabetic care

ACKNOWLEDGEMENT

The skilful assistance of Hannelore Claesson and Madeleine Svensson is gratefully acknowledged

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Acta Med Scand Suppl 656: 69 1981

Characteristic Lesions Localized to the Lower Limbs in Patients with Open and Not Open Diabetes

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e diagnosis of diabetes can often be made rough clinical examination. Diabetic lesions, pecially skin lesions on the lower extremities, ve been studied at our Department of Medicine r 20 years. In our opinion there are certain le ons in the lower extremities wich are more or less haracteristic of diabetes:

1. Cutaneous erythema without or with necro- s incipient or manifest gangrene (1 3 4 5 6)
2. Destruction of the bones of the feet = diabetic steopathy (1 3 4).
3. Rubeosis plantarum, including red toes (see Lithner (1)).
4. Bullosis diabeticorum (see Lithner (4)).
5. Skin spots (7).
6. Purpura (2, 5).
7. Yellow toe nails (2).
8. Necrobiosis lipoidica diabeticorum
9. Peripheral polyneuropathy

Most of the patients with incipient or manifest gangrene (1 3, 5 6), skeletal destruction of the feet (3), skin spots (7), purpura (2) and yellow toe nails (2) had open diabetes while the remaining patients had oral glucose tolerance test curve areas significantly altered in a diabetic direction when compared with an unselected control group (1). Many patients with so-called non-open diabetes later developed open diabetes.

The diagnosis of diabetes in patients without glucosuria, especially in the elderly can very often be made with a great certainty only by inspection of the lower extremities.

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The diagnosis of diabetes can often be made through clinical examination. Diabetic lesions especially skin lesions on the lower extremities have been studied at our Department of Medicine for 20 years. In our opinion there are certain lesions in the lower extremities which are more or less characteristic of diabetes:

1 Cutaneous erythema without or with necrosis = incipient or manifest gangrene (1 3 4 5 6)

2. Destruction of the bones of the feet = diabetic osteopathy (1 3 4).

3 Rubeosis plantarum, including red toes (see Lithner (1)).

4 Bullosis diabeticorum (see Lithner (4)).

5 Shin spots (7)

6 Purpura (2, 5)

7 Yellow toe nails (2)

8 Necrobiosis lipoidica diabeticorum.

9 *Peripheral polyneuropathy*

Most of the patients with incipient or manifest gangrene (1 3 5 6) skeletal destruction of the feet (3), shin spots (7) purpura (2) and yellow toe nails (2) had open diabetes while the remaining patients had oral *glucose tolerance test curve* *were significantly* altered in a diabetic direction when compared with an unselected control group (1). Many patients with so-called non-open diabetes later developed open diabetes

The diagnosis of diabetes in patients without glucosuria, especially in the elderly can very often be made with a great certainty only by inspection of the lower extremities.

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